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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

COSMO TECHNOLOGIES LIMITED and SANTARUS, INC., Plaintiffs, v. ACTAVIS LABORATORIES FL, INC., Defendant.	)	Civil Action No. __________

COMPLAINT

Plaintiffs Cosmo Technologies Limited ("Cosmo") and Santarus, Inc. ("Santarus") (collectively, "Plaintiffs"), for their Complaint against Defendant Actavis Laboratories FL, Inc.

("Actavis"), hereby allege as follows:

PARTIES

1. Plaintiff Cosmo is an Irish corporation, having its principal place of business at Connolly Building, 42-43 Amiens Street, Dublin, Ireland.

2. Plaintiff Santarus is a Delaware corporation, having its principal place of business at 8510 Colonnade Center Drive, Raleigh, North Carolina 27615.

3. Upon information and belief, Actavis is a corporation organized and existing under the laws of Florida, having its principal place of business at 400 Interpace Parkway, Parsippany, New Jersey 07054. On information and belief, Defendant Actavis develops, manufactures, and packages numerous generic versions of branded pharmaceutical products for sale and use in the State of New Jersey and throughout the United States.

NATURE OF THE ACTION

4. This is a civil action for infringement of U.S. Patent No. 7,410,651 ("the '651 patent"); U.S. Patent No. 7,431,943 ("the '943 patent"); U.S. Patent No. 8,293,273 ("the '273 patent"); U.S. Patent No. 8,784,888 ("the '888 patent"); U.S. Patent No. 8,895,064 ("the '064 patent"); and U.S. Patent RE 43,799 ("the '799 patent") (collectively, the "patents-in-suit"). This action arises under the Patent Laws of the United States, 35 U.S.C. § 100 *et seq*.

JURISDICTION AND VENUE

5. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

6. This Court has personal jurisdiction over Defendant Actavis because Actavis maintains its principal place of business at 400 Interpace Parkway, Parsippany, New Jersey 07054, and by virtue of, *inter alia*, having availed itself of the rights and benefits of

New Jersey law and having engaged in systematic and continuous contacts with the State of New Jersey.

7. This Court has personal jurisdiction over Defendant Actavis by virtue of, *inter alia*, the fact that it has committed, or aided, abetted, contributed to, and/or participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs in this State.

8. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENTS-IN-SUIT

9. On August 12, 2008, the '651 patent, titled "Controlled Release and Taste Masking Oral Pharmaceutical Composition," was duly and legally issued. A copy of the '651 patent is attached hereto as Exhibit A.

10. Cosmo is the present owner of the '651 patent. Santarus holds an exclusive license to the '651 patent.

11. On October 7, 2008, the '943 patent, titled "Controlled Release and Taste Masking Oral Pharmaceutical Composition," was duly and legally issued. A copy of the '943 patent is attached hereto as Exhibit B.

12. Cosmo is the present owner of the '943 patent. Santarus holds an exclusive license to the '943 patent.

13. On October 23, 2012, the '273 patent, titled "Controlled Release and Taste Masking Oral Pharmaceutical Composition," was duly and legally issued. A copy of the '273 patent is attached hereto as Exhibit C.

14. Cosmo is the present owner of the '273 patent. Santarus holds an exclusive license to the '273 patent.

15. On July 22, 2014, the '888 patent, titled "Controlled Release and Taste Masking Oral Pharmaceutical Composition," was duly and legally issued. A copy of the '888 patent is attached hereto as Exhibit D.

16. Cosmo is the present owner of the '888 patent. Santarus holds an exclusive license to the '888 patent.

17. On November 25, 2014, the '064 patent, titled "Controlled Release and Taste Masking Oral Pharmaceutical Composition," was duly and legally issued. A copy of the '064 patent is attached hereto as Exhibit E.

18. Cosmo is the present owner of the '064 patent. Santarus holds an exclusive license to the '064 patent.

19. On November 13, 2012, the '799 patent, titled "Controlled Release and Taste Masking Oral Pharmaceutical Composition," was duly and legally reissued. A copy of the '799 patent is attached hereto as Exhibit F.

20. Cosmo is the present owner of the '799 patent. Santarus holds an exclusive license to the '799 patent.

ACTS GIVING RISE TO THIS ACTION

21. Santarus holds New Drug Application ("NDA") No. 203634 for oral tablets containing 9 mg of the active ingredient budesonide, which are sold in the United States under the brand name "Uceris®." Uceris® is indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis.

22. Pursuant to 21 U.S.C. § 355(b)(1), the '651 patent, the '943 patent, the '273 patent, the '888 patent, the '064 patent, and the '799 patent are listed in the U.S. Food and Drug Administration's ("FDA") publication titled *Approved Drug Products with Therapeutic*

Equivalence Evaluations (also known as the "Orange Book") as covering Uceris® and its method of use.

23. Upon information and belief, Actavis submitted Abbreviated New Drug Application ("ANDA") No. 205457 ("Actavis's ANDA") to the FDA under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)). Upon information and belief, Actavis's ANDA seeks FDA approval to engage in the commercial manufacture, use, sale, or offer for sale of tablets containing 9 mg of budesonide ("Actavis Generic Product") prior to the expiration of the '651 patent, the '943 patent, the '273 patent, the '888 patent, the '064 patent, and the '799 patent.

24. Upon information and belief, pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, Actavis certified in ANDA No. 205457, *inter alia*, that the claims of the '651 patent, the '943 patent, the '273 patent, the '888 patent, the '064 patent, and the '799 patent are invalid, unenforceable, and/or would not be infringed by the commercial manufacture, use, offer for sale, or sale of the Actavis Generic Product.

25. Plaintiffs received written notification of Actavis's ANDA and its accompanying § 505(j)(2)(A)(vii)(IV) certification by a letter dated January 5, 2015, ("Actavis's Notice Letter") and sent via Federal Express.

26. This action was commenced by Plaintiffs within 45 days of the date of the receipt of Actavis's Notice Letter.

27. Actavis's Notice Letter included an accompanying Offer of Confidential Access ("OCA") to certain Actavis confidential information regarding the Actavis Generic Product. Over the course of several weeks, Plaintiffs negotiated with Actavis in an effort to agree on reasonable terms for Actavis's OCA. The parties were not able to reach an agreement with respect to Plaintiffs' proposed revisions to Actavis's OCA.

28. To date, Actavis has not provided Plaintiffs with a copy of any portions of its ANDA or any information regarding the Actavis Generic Product, beyond the information that was set forth in Actavis's Notice Letter.

29. The limited information relating to the Actavis Generic Product that was provided in Actavis's Notice Letter does not demonstrate that the Actavis Generic Product that Actavis is asking the FDA to approve for sale in the United States will not fall within the scope of any issued claim of the '651 patent, the '943 patent, the '273 patent, the '888 patent, the '064 patent, or the '799 patent.

FIRST COUNT
INFRINGEMENT BY ACTAVIS OF U.S. PATENT NO. 7,410,651

30. Plaintiffs re-allege paragraphs 1-29 as if fully set forth herein.

31. Actavis's submission of ANDA No. 205457 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification, constitutes infringement of the '651 patent under 35 U.S.C. § 271(e)(2)(A).

32. Moreover, if Actavis manufactures, uses, sells, offers for sale, or imports into the United States any of the Actavis Generic Product, or induces or contributes to any such conduct, prior to the expiration of the '651 patent, including any applicable exclusivities or extensions, Actavis would further infringe the '651 patent under 35 U.S.C. § 271(a), (b), and/or (c).

33. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Actavis's ANDA No. 205457 be a date that is not earlier than the expiration of the term of the '651 patent, including any extension(s) granted by the U.S. Patent and Trademark Office ("PTO") pursuant

to 35 U.S.C. §§ 154 or 156, or any later expiration of exclusivity for the '651 patent to which Plaintiffs are or become entitled.

34. Plaintiffs will be irreparably harmed by Actavis's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

35. Upon information and belief, Actavis was aware of the existence of the '651 patent and was aware that the filing of its ANDA and accompanying § 505(j)(2)(A)(vii)(IV) certification with respect to the '651 patent constituted an act of infringement of the '651 patent.

SECOND COUNT
INFRINGEMENT BY ACTAVIS OF U.S. PATENT NO. 7,431,943

36. Plaintiffs re-allege paragraphs 1-35 as if fully set forth herein.

37. Actavis's submission of ANDA No. 205457 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification, constitutes infringement of the '943 patent under 35 U.S.C. § 271(e)(2)(A).

38. Moreover, if Actavis manufactures, uses, sells, offers for sale, or imports into the United States any of the Actavis Generic Product, or induces or contributes to any such conduct, prior to the expiration of the '943 patent, including any applicable exclusivities or extensions, Actavis would further infringe the '943 patent under 35 U.S.C. § 271(a), (b), and/or (c).

39. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Actavis's ANDA No. 205457 be a date that is not earlier than the expiration of the term of the '943 patent,

including any extension(s) granted by the PTO pursuant to 35 U.S.C. §§ 154 or 156, or any later expiration of exclusivity for the '943 patent to which Plaintiffs are or become entitled.

40. Plaintiffs will be irreparably harmed by Actavis's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

41. Upon information and belief, Actavis was aware of the existence of the '943 patent and was aware that the filing of its ANDA and accompanying § 505(j)(2)(A)(vii)(IV) certification with respect to the '943 patent constituted an act of infringement of the '943 patent.

THIRD COUNT
INFRINGEMENT BY ACTAVIS OF U.S. PATENT NO. 8,293,273

42. Plaintiffs re-allege paragraphs 1-41 as if fully set forth herein.

43. Actavis's submission of ANDA No. 205457 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification, constitutes infringement of the '273 patent under 35 U.S.C. § 271(e)(2)(A).

44. Moreover, if Actavis manufactures, uses, sells, offers for sale, or imports into the United States any of the Actavis Generic Product, or induces or contributes to any such conduct, prior to the expiration of the '273 patent, including any applicable exclusivities or extensions, Actavis would further infringe the '273 patent under 35 U.S.C. § 271(a), (b), and/or (c).

45. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Actavis's ANDA No. 205457 be a date that is not earlier than the expiration of the term of the '273 patent,

including any extension(s) granted by the PTO pursuant to 35 U.S.C. §§ 154 or 156, or any later expiration of exclusivity for the '273 patent to which Plaintiffs are or become entitled.

46. Plaintiffs will be irreparably harmed by Actavis's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

47. Upon information and belief, Actavis was aware of the existence of the '273 patent and was aware that the filing of its ANDA and accompanying § 505(j)(2)(A)(vii)(IV) certification with respect to the '273 patent constituted an act of infringement of the '273 patent.

FOURTH COUNT
INFRINGEMENT BY ACTAVIS OF U.S. PATENT NO. 8,784,888

48. Plaintiffs re-allege paragraphs 1-47 as if fully set forth herein.

49. Actavis's submission of ANDA No. 205457 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification, constitutes infringement of the '888 patent under 35 U.S.C. § 271(e)(2)(A).

50. Moreover, if Actavis manufactures, uses, sells, offers for sale, or imports into the United States any of the Actavis Generic Product, or induces or contributes to any such conduct, prior to the expiration of the '888 patent, including any applicable exclusivities or extensions, Actavis would further infringe the '888 patent under 35 U.S.C. § 271(a), (b), and/or (c).

51. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Actavis's ANDA No. 205457 be a date that is not earlier than the expiration of the term of the '888 patent,

including any extension(s) granted by the PTO pursuant to 35 U.S.C. §§ 154 or 156, or any later expiration of exclusivity for the '888 patent to which Plaintiffs are or become entitled.

52. Plaintiffs will be irreparably harmed by Actavis's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

53. Upon information and belief, Actavis was aware of the existence of the '888 patent and was aware that the filing of its ANDA and accompanying § 505(j)(2)(A)(vii)(IV) certification with respect to the '888 patent constituted an act of infringement of the '888 patent.

FIFTH COUNT
INFRINGEMENT BY ACTAVIS OF U.S. PATENT NO. 8,895,064

54. Plaintiffs re-allege paragraphs 1-53 as if fully set forth herein.

55. Actavis's submission of ANDA No. 205457 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification, constitutes infringement of the '064 patent under 35 U.S.C. § 271(e)(2)(A).

56. Moreover, if Actavis manufactures, uses, sells, offers for sale, or imports into the United States any of the Actavis Generic Product, or induces or contributes to any such conduct, prior to the expiration of the '064 patent, including any applicable exclusivities or extensions, Actavis would further infringe the '064 patent under 35 U.S.C. § 271(a), (b), and/or (c).

57. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Actavis's ANDA No. 205457 be a date that is not earlier than the expiration of the term of the '064 patent,

including any extension(s) granted by the PTO pursuant to 35 U.S.C. §§ 154 or 156, or any later expiration of exclusivity for the '064 patent to which Plaintiffs are or become entitled.

58. Plaintiffs will be irreparably harmed by Actavis's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

59. Upon information and belief, Actavis was aware of the existence of the '064 patent and was aware that the filing of its ANDA and accompanying § 505(j)(2)(A)(vii)(IV) certification with respect to the '064 patent constituted an act of infringement of the '064 patent.

SIXTH COUNT
INFRINGEMENT BY ACTAVIS OF U.S. PATENT RE 43,799

60. Plaintiffs re-allege paragraphs 1-59 as if fully set forth herein.

61. Actavis's submission of ANDA No. 205457 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification, constitutes infringement of the '799 patent under 35 U.S.C. § 271(e)(2)(A).

62. Moreover, if Actavis manufactures, uses, sells, offers for sale, or imports into the United States any of the Actavis Generic Product, or induces or contributes to any such conduct, prior to the expiration of the '799 patent, including any applicable exclusivities or extensions, Actavis would further infringe the '799 patent under 35 U.S.C. § 271(a), (b), and/or (c).

63. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Actavis's ANDA No. 205457 be a date that is not earlier than the expiration of the term of the '799 patent,

including any extension(s) granted by the PTO pursuant to 35 U.S.C. §§ 154 or 156, or any later expiration of exclusivity for the '799 patent to which Plaintiffs are or become entitled.

64. Plaintiffs will be irreparably harmed by Actavis's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

65. Upon information and belief, Actavis was aware of the existence of the '799 patent and was aware that the filing of its ANDA and accompanying § 505(j)(2)(A)(vii)(IV) certification with respect to the '799 patent constituted an act of infringement of the '799 patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. That Actavis has infringed one or more claims of the '651 patent;

B. That Actavis has infringed one or more claims of the '943 patent;

C That Actavis has infringed one or more claims of the '273 patent;

D That Actavis has infringed one or more claims of the '888 patent;

E That Actavis has infringed one or more claims of the '064 patent;

F That Actavis has infringed one or more claims of the '799 patent;

G. That pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 205457 under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall not be a date that is earlier than the latest expiration date of the patents-in-suit, including any applicable exclusivities or extensions;

H. That Actavis, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering to sell, selling, or importing into the United States

the Actavis Generic Product and any other product that infringes or induces or contributes to the infringement of one or more claims of the '651 patent, the '943 patent, the '273 patent, the '888 patent, the '064 patent, and the '799 patent prior to their expiration, including any exclusivities or extensions to which Plaintiffs are or become entitled;

I. That Plaintiffs be awarded the attorney fees, costs, and expenses that they incur prosecuting this action; and

J. That Plaintiffs be awarded such other and further relief as this Court deems just and proper.

Dated: February 19, 2015

By: s/ Charles M. Lizza

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matters captioned *Cosmo Technologies Limited, et al. v. Par Pharmaceutical, Inc.*, Civil Action No. 15-116 (D. Del.) and *Cosmo Technologies Limited, et al. v. Actavis Laboratories FL, Inc.* (D. Del.), which was filed on February 17, 2015, are related to the matter in controversy because the matter in controversy involves the same plaintiffs and the same patents. I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Respectfully submitted,

Dated: February 19, 2015

By: s/ Charles M. Lizza

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Attorneys for Plaintiffs Cosmo Technologies Limited and Santarus, Inc.

EXHIBIT A

US007410651B2

(12) **United States Patent**
Villa et al.

(10) **Patent No.:** **US 7,410,651 B2**
(45) **Date of Patent:** **Aug. 12, 2008**

(54) **CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION**

(75) Inventors: **Roberto Villa**, Lecco (IT); **Massimo Pedrani**, Gignese (IT); **Mauro Ajani**, Milan (IT); **Lorenzo Fossati**, Milan (IT)

(73) Assignee: **Cosmo Technologies Limited**, Wicklow (IE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **11/268,500**

(22) Filed: **Nov. 8, 2005**

(65) **Prior Publication Data**

US 2006/0134208 A1 Jun. 22, 2006

Related U.S. Application Data

(63) Continuation-in-part of application No. 11/262,799, filed on Nov. 1, 2005, now abandoned, which is a continuation-in-part of application No. 10/009,532, filed as application No. PCT/EP00/05356 on Jun. 9, 2000.

(30) **Foreign Application Priority Data**

Jun. 14, 1999 (IT) MI99A1317
Mar. 3, 2000 (IT) MI2000A0422

(51) **Int. Cl.**
A61K 9/22 (2006.01)
A61K 9/48 (2006.01)
A61K 9/20 (2006.01)
A61K 9/26 (2006.01)

(52) **U.S. Cl.** **424/468**; 424/451; 424/464; 424/465; 424/469; 424/470

(58) **Field of Classification Search** 424/451, 424/464
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,342,625 A *	8/1994	Hauer et al.
5,597,844 A	1/1997	Chauhan et al.
6,190,692 B1 *	2/2001	Busetti et al.
6,368,635 B1	4/2002	Akiyama et al.

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EP	0 514 008 A1		11/1992
GB	935639		9/1963
WO	96/13273	*	5/1996
WO	WO 99/11245		3/1999
WO	WO 99/17752		4/1999

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"Budesonide"—Wikipedia, the free enclycopedia (http://en.wikipedia.org/wiki/Budesonide); pp. 1-3.*

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Primary Examiner—Humera N Sheikh
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(57) **ABSTRACT**

Controlled release and taste masking compositions containing one or more active principles inglobated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally inglobated or dispersed in hydrophilic matrices. The use of a plurality of systems for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract.

11 Claims, No Drawings

CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION

The present invention relates to controlled release and taste masking compositions containing budesonide as active ingredient incorporated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally incorporated or dispersed in hydrophilic matrices. The use of a plurality of systems mechanism for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract, and it also allows the oral administration of active principles having unfavourable taste characteristics or irritating action on the mucosae of the administration site, particularly in the buccal or gastric area.

The compositions of the invention are suitable to the oral administration or the efficaciously deliver the active ingredient acting topically at some areas of the gastrointestinal tract.

TECHNOLOGICAL BACKGROUND

The preparation of a sustained, controlled, delayed, extended or anyhow modified release form can be carried out according to different techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of bioerodible matrices, which are capable of being degraded by the anzimes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Inert matrices, for example, generally entail non-linear, but exponential, release of the active ingredient.

Hydrophilic matrices: have a linear behaviour until a certain fraction of active ingredient has been released, then significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "sire-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated

The same notion of canalization of an inert matrix is described in U.S. Pat. No. 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials. EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form. The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3),531-533, (1998) which improves the application through an annealing technique of the inert polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in bydrophilic matrix which comprises: -dissolution of the active ingredient with gastro resistant hydrophilic polymers in organic solvents; -diying of said suspension; -subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application. EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid. WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of the active ingredient. When preparing sustained-, controlled-release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release. Said object has been attained according to the present invention, through the combination of an amphiphilic matrix inside an inert matrix, the latter formulated with a lipophilic polymer in a superficial hydrophilic matrix. The compositions of the invention are characterized by the absence of a first phase in which the medicament superficially present on the matrix is quickly solubilized, and by the fact the amphiphilic layer compensate the lack of affinity of the aqueous solvent with the lipophilic compounds forming the inner inert matrix.

DISCLOSURE OF THE INVENTION

The invention provides controlled release and taste masking oral pharmaceutical compositions containing as active ingredient budesonide comprising:

a) a matrix consisting of lipophilic compounds with melting point lower than 90° C. and optionally by amphiphilic compounds in which the active ingredient is at least partially incorporated;

b) an amphiphilic matrix;

c) an outer hydrophilic matrix in which the lipophilic matrix and the amphiphilic matrix are dispersed;

d) optionally other excipients.

A particular aspect of the invention consists of controlled release oral compositions containing as active ingredient budesonide comprising:

a) a matrix consisting of amphiphilic compounds and lipophilic compounds with melting point below 90° C. in which the active ingredient is at least partially incorporated;

b) an outer hydrophilic matrix in which the lipophilic/amphiphilic matrix is dispersed, preferably by mixing;

c) optionally other excipients.

A further aspect of the invention provides taste masking oral pharmaceutical compositions budesonide containing comprising:

an inert or lipophilic matrix consisting of C6-C20 alcohols or C8-C20 fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six:

an amphiphilic matrix consisting of polar lipids of type I or II or glycols partially etherified with C1-C4 alkyl chains;

an outer hydrophilic matrix containing the above matrices, mainly formed by saccharide, dextrin, polyalcohol or cellulose compounds or by hydrogels or their mixtures;

optional excipients to give stability to the pharmaceutical formulation.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be prepared by a method comprising the following steps:

a) the active ingredient, represented by budesonide, is first inglobated by simple kneading or mixing in a matrix or coating consisting of compounds having amphiphilic properties, which will be further specified below. The active ingredient can be mixed with the amphiphilic compounds without the aid of solvents or with small amounts of water-alcoholic solvents.

b) the matrix obtained as specified under a) is incorporated in a low melting lipophilic excipient or mixture of excipients, if necessary while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion forming an inert matrix which can be reduced in size to obtain inert matrix granules containing the active ingredient particles.

c) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients. The mixture is then subjected to compression or tabletting. This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix. The amphiphilic compounds which can be used according to the invention comprise polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolainine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol^R) The lipophilic matrix consists of substances selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, fatty acids mono-, di-or triglycerids, the polyethoxylated derivatives thereof, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40 to 90 C, preferably from 60 to 70 C. If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside. An amphiphilic matrix with high content in active ingredient, typically from 5 to 95% w/w, in particular from 20 to 70%, is first prepared by dispersing the active ingredient in a mixture of amphiphilic compounds, such as lecithin, other type II polar lipids, surfactants, or in diethylene glycol monoethyl ether; the resulting amphiphilic matrix is then mixed or Icneaded, usually while hot, with lipophilic compounds suitable to form an inert matrix, such as saturated or unsaturated fatty acids, such as palmitic, stearic, myristic, lauric, laurylic, or oleic acids or mixtures thereof with other fatty acids with shorter chain, or salts or alcohols or derivatives of the cited fatty acids, such as mono-, di-, or triglycerids or esters with polyethylene glycols, alone or in combination with waxes, ceramides, cholesterol derivatives or other apolar lipids in various ratios so that the melting or softening points of the lipophilic compounds mixtures is within the range of 40 to 90 C, preferably from 60 to 70 C. Alternatively, the order of formation of the inert and amphiphilic matrices can be reversed, incorporating the inert matrix inside the amphiphilic compounds. The resulting inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture. The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which when passing from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves. Examples of hydrogels which can be used according to the invention are compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid. In case of taste-masking formulations, the use of polyalcohols such as xylitol, maltitol and mannitol as hydrophilic compounds can also be advantageous. The lipophilic matrix granules containing the active ingredient are mixed with the hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:50 (lipophilic matrix: hydrophilic matrix). Part of the active ingredient can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitablets. The compression of the mixture of lipophilic and/or amphiphilic matrix, hydrogel-forming compound and, optionally, active ingredient not inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix. A similar result can also be obtained by coating the lipophilic matrix granules with a hydrophilic polymer coating. The tablets obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of, for example, acrylic and methacrylic acids polymers(Eudragit (R)) or copolymer or cellulose derivatives, such as cellulose acetophthalate. The composition of the invention can further contain conventional excipients, for example bioadhesive excipients such as chitosans, polyacrylamides, natural or synthetic gums, acrylic acid polymers.

The compositions of the invention are preferably in the form of tablets, capsules or minitablets. In terms of dissolution characteristics, contact with water or aqueous fluids causes the immediate penetration of water inside the more superficial layer of the matrix which, thanks to the presence of the aqueous solvent, swells due to the distension of the poly-

meric chains of the hydrogels, giving rise to a high viscosity hydrated front which prevents the further penetration of the solvent itself linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness, until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of inert matrix granules, however induces the diffusion mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient. The presence of the amphiphilic matrix inside the lipophilic matrix inert allows to prevent any unevenness of the release profile of the active ingredient. The surfactants present in the amphiphilic portion promote wettability of the porous canaliculuses which cross the inert matrix preventing or reducing resistance to penetration of the solvent inside the inert matrix. To obtain taste masking tablets, the components of the hydrophilic matrix are carefully selected to minimize the active substance release time through penetration accelerated by the canalization induced by the hydrophilic compound.

EXPERIMENTAL PART

To test the effective ability of the formulations of the invention to modify the release rate and extent of the active ingredient from the dosage form suitable for the drug administration, before any pharmacokinetic study on patients or volunteers, the dissolution test is taken as monitoring and discriminating tool.

Dissolution Test Method

Tablets according to the present invention undergo to dissolution test to verify the formulation capacity in modulating and controlling the rate by which the active ingredient is leaked by the device or dosage form in the environmental medium, generally a buffered solution simulating gastric or intestinal juices.

The dissolution test is performed by introducing individual tablets in a glace vessel containing from 500 to 1000 ml of a buffered solution set to different pH conditions (pH 1, 6.4 and 7.2 are the pH condition generally used in this test applications), so that the whole digestive tract pH conditions, from stomach to large intestine, should be reproduced. To simulate the human body conditions, the test is carried out at a temperature of 37° C.±2° C. and at predetermined time periods samples of the dissolution medium are withdrawn to detect the percentage of active ingredient dissolved over time.

The tablets according to the present invention, when designed to be used to treat inflammatory bowel disease, in principle have to show a good resistance, thanks to the polymeric film resistant to the low pH conditions (intended as <5 to simulate the gastric environment) applied to cover the tablet surface, resistance which last at least for two hours; to target the large intestinal sectors, also the pH condition of 6.4 shown unsuitability to determine a drug leakage from the administration device for a short exposition time and only mediums at pH 7.2 have been able to determine an active ingredient dissolution at a progressive and quite constant rate during a timeframe from 6 to 12 hours; the dissolution percentage obtained with this tablet formulation were below 15% at first hour sampling, below 25% at second hour sampling, then values were in the range 25% to 55% at fourth hour and a dissolution greater than 80% was achieved at 8th hour sampling.

EXAMPLE 1

2.7 kg of budesonide, 3.0 kg of lecithin (amphiphilic matrix forming material) and 3.0 kg of stearic acid (lipophilic matrix forming material) are mixing after sieving till an homogeneous mixture is obtained; then add 39.0 kg of inert, functional excipients and 9.0 kg of low viscosity hydroxypropylcellulose (binder) and mix for 10 minutes before adding purified water and kneading to a suitable consistence. Then pass the granulate through a rotating granulator equipped with the suitable screen and transfer the granulate to the fluid bed drier to lower the residual moisture content under 3%.

After a new sieving on the dry, the granulate is added of 9.0 kg of hydroxypropylcellulose (hydrophilic matrix forming material) and the suitable amount of functional excipients (in particular, microcrystalline cellulose, lactose and silicon dioxide)

and, after 15 minutes of mixing, magnesium stearate in a suitable quantity to act as lubricant is added.

After a final blending, tablets of around 300 mg of unitary weight are generated.

The core are then subjected to be coated with a suspension obtained introducing into a stainless steel container 5.8 kg of Eudragit™ (methacrylate copolymers), 0.6 kg of triethylcitrate and 3.0 kg of dyes and talc, using alcohol as solvent.

The mean dissolution percentage (as average of six or more tablets) obtained with this tablet formulation were around 10-20% at second hour sampling, in the range 25% to 65% at fourth hour and a dissolution greater than 80% was achieved at 8th hour sampling.

EXAMPLE 2

Component	mg/tablet
Tablet	
Budesonide	9.0
Stearic Acid	10.0
Lecithin	10.0
Microcristalline cellulose	156.0
Hydroxypropylcellulose	60.0
Lactose monohydrate	50.0
Silicon dioxide	2.0
Magnesium stearate	3.0
Coating materials	
Eudragit L100	14.0
Eudragit S100	12.0
Talc	7.9
Titanium dioxiede	4.5
Triethylcitrate	1.6
Alcohol	q.s.

According to the present invention, coated tablets individually weighing about 220 mg are obtained.

The above described dissolution test is performed on the tablets of Example 2.

The results are the following (indicated as average value):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	15%
after 4 hours at pH 7.2	37%
after 8 hours at pH 7.2	91%

EXAMPLE 3

Budesonide (3.0 kg) is mixed with soybean Lecithin (5.0 kg) till an homogeneous mixture is obtained. Then carnauba wax (2.0 kg) and stearic acid (2.0 kg) sieved through a fine screen are added. After mixing, the powders are added with other functional excipients and kneaded with a binder solution obtained by dissolving medium viscosity polyvinylpirrolidone in water. After drying in a fluid bed and milling throughout a suitable screen, hydroxypropylmethylcellulose (35.0 kg) and other excipients, including magnesium stearate as lubricant, in a suitable quantity are added and the mixture is blended till an homogeneous powder dispersion is obtained.

The powder mixture is subjected to compression in a rotating tabletting machine and the tablets so obtained are coated in a pan coat with a gastroresistant composition containing Eudragit™, plasticizers, dyes and pigments.

According to the present example, coated tablets individually weighing around 105 mg are obtained.

The results of the above described dissolution test are the following (indicated as average value of at least six tablets):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	9%
after 4 hours at pH 7.2	28%
after 8 hours at pH 7.2	86%

EXAMPLE 4

50 g of diethylene glycol monoethyl ether are homogeneously distributed on 500 g of microcrystalline cellulose; then 100 g of Budesonide are added, mixing to complete homogenization. This mix is further added with 400 g of Budesonide, then dispersed in a blender containing 100 g of carnauba wax and 100 g of stearic acid preheated at a temperature of 60° C. After kneading for 5 minutes, the mixture is cooled to room temperature and extruded in granules of size below 1 mm. A suitable mixer is loaded with the matrix granules prepared as above and the following amounts of hydrophilic excipients: 1500 g of hydroxypropyl methylcellulose and 500 g of Policarbophil™ are added. The components are mixed until homogeneous dispersion of the matrices, then added with 2450 g of microcrystalline cellulose, 400 g of lactose, 100 g of colloidal silica and 50 g of magnesium stearate. After further 5 minute mixing, the mix is tabletted to unitary weight of 250 mg/tablet.

Tablets are then subjected to coating using a suspension n containing polyacrylate and poly methacrilate copolymers in addition to other dyes, plasticizers and colouring agents in solvent (ethylic alcohol).

The results of the dissolution test performed on these coated tablets are the following (indicated as average value of at least six tablets):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	11%
after 4 hours at pH 7.2	32%
after 8 hours at pH 7.2	76%

The invention claimed is:

1. A controlled release oral pharmaceutical composition containing budesonide as active ingredient consisting essentially of:

a) a lipophilic matrix consisting of lipophilic compounds with a melting point between 40° C. and 90 C. in which the active ingredient is at least partially inglobated;

b) an amphiphilic matrix;

c) an outer hydrophilic matrix consisting of hydrogel forming compounds in which the lipophilic matrix and the amphiphilic matrix are dispersed, wherein the combination of the matrices from a), b), and c) provides controlled release.

2. The composition according to claim **1** in which the active ingredient is mixed and at least partially inglobated in the amphiphilic matrix of point b).

3. The composition according to claim **1**, wherein the active ingredient is mixed and at least partially inglobated in the lipophilic matrix.

4. The composition according to claim **1**, wherein, the lipophilic matrix consists of compounds selected from the group consisting of C6-C 20 alcohols, C8-C 20 fatty acids, and esters of fatty acids with, glycerol, sorbitol or other polyalcohols with carbon atom chain not higher than six.

5. The composition according to claim **1**, wherein the amphiphilic compounds are selected from the group consisting of polar lipids of type I or II, ceramides, glycol alkyl ethers, esters of fatty acids with polyethylene glycols, and diethylene glycols.

6. The composition according to claim **1**, wherein the lipophilic matrix consists of a compound selected from the group consisting of unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof; mono-, di- or triglycerides of fatty acids, polyethoxylated derivatives thereof; waxes; and cholesterol derivatives.

7. The composition according to claim **1**, wherein the hydrophilic matrix consists of compounds selected from the group consisting of acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkylcellulose, carboxyalkylcellulose, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums, and polyalcohols.

8. The composition according to claim **1**, wherein the active ingredient is wholly contained in the lipophilic/amphiphilic matrix, in the form of tablets, capsules or minitablets.

9. The composition according to claim **1**, wherein the active ingredient is dispersed both in the hydrophilic matrix and in the lipophilic/amphiphilic matrix, in the form of tablets, capsules or minitablets.

10. The composition according to claim **1**, wherein said composition is in the form of tablets chewable or erodible in the buccal cavity or in the first portion of the gastrointestinal tract.

11. A method for the treatment of Inflammatory Bowel Disease and Irritable Bowel Syndrome, comprising administering the composition according to claim **1** to a patient in need of such a treatment.

* * * * *

EXHIBIT B

US007431943B1

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(54) **CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITIONS**

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See application file for complete search history.

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(57) **ABSTRACT**

Controlled release and taste masking compositions containing one or more active principles inglobated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally inglobated or dispersed in hydrophilic matrices. The use of a plurality of systems for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract.

13 Claims, No Drawings

CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITIONS

The present invention relates to controlled release and taste-masking compositions containing one or more active principles incorporated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally incorporated or dispersed in hydrophilic matrices. The use of a plurality of systems for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract, and it also allows the oral administration of active principles having unfavourable taste characteristics or irritating action on the mucosae of the administration site, particularly in the buccal area.

The compositions of the invention can contain active principles belonging to the therapeutical classes of analgesics, antiinflammatories, cardioactives, tranquillizers, antihypertensives, disinfectants and topical antimicrobials, antiparkinson drugs, antihistamines and are suitable to the oral administration or for acting topically at some areas of the gastrointestinal tract.

TECHNOLOGICAL BACKGROUND

The preparation of a sustained, controlled, delayed or anyhow modified release form can be carried out according to different known techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of bioerodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Inert matrices, for example, generally entail non-linear, but exponential, release of the active ingredient.

Hydrophilic matrices have a linear behaviour until a certain fraction of active ingredient has been released; then they significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "site-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated.

The same notion of canalization of an inert matrix is described in U.S. Pat. No. 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials.

EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form.

The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533, (1998) which improves the application through an annealing technique of the inert polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises:

- dissolution of the active ingredient with gastro-resistant hydrophilic polymers in organic solvents;
- drying of said suspension;
- subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application.

EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid.

WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of the active ingredient.

When preparing sustained-, controlled-release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release.

Said object has been attained according to the present invention, through the combination of an amphiphilic matrix inside an inert matrix, the latter formulated with a lipophilic polymer in a superficial hydrophilic matrix. The compositions of the invention are characterized by the absence of a first phase in which the medicament superficially present on the matrix is quickly solubilized, and by the fact the amphiphilic layer compensate the lack of affinity of the aqueous solvent with the lipophilic compounds forming the inner inert matrix.

DISCLOSURE OF THE INVENTION

The invention provides controlled release and taste masking oral pharmaceutical compositions containing an active ingredient, comprising:

a) a matrix consisting of lipophilic compounds with melting point lower than 90° C. and optionally by amphiphilic compounds in which the active ingredient is at least partially incorporated;

b) optionally an amphiphilic matrix;

c) an outer hydrophilic matrix in which the lipophilic matrix and the optional amphiphilic matrix are dispersed;

d) optionally other excipients.

A particular aspect of the invention consists of controlled release oral compositions containing one or more active ingredients comprising:

a) a matrix consisting of amphiphilic compounds and lipophilic compounds with melting point below 90° C. in which the active ingredient is at least partially incorporated;

b) an outer hydrophilic matrix in which the lipophilic/amphiphilic matrix is dispersed;

c) optional other excipients.

A further aspect of the invention provides taste masking oral pharmaceutical compositions containing one or more active ingredients comprising:

- an inert or lipophilic matrix consisting of C6-C20-alcohols or C8-C20 fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six;
- an amphiphilic matrix consisting of polar lipids of type I or II or glycols partially etherified with C1-C4 alkyl chains;
- an outer hydrophilic matrix containing the above matrices, mainly formed by saccharide, dextrin, polyalcohol or cellulose compounds or by hydrogels;
- optional excipients to give stability to the pharmaceutical formulation.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be prepared by a method comprising the following steps:

a) the active ingredient is first inglobated by simple kneading or mixing in a matrix or coating consisting of compounds having amphiphilic properties, which will be further specified below. The active principle(s) can be mixed with the amphiphilic compounds without the aid of solvents or with small amounts of water-alcoholic solvents.

b) The matrix obtained in a) is incorporated in a low melting lipophilic excipient or mixture of excipients, while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion. After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain inert matrix granules containing the active ingredient particles.

c) The inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients. The mixture is then subjected to compression or tabletting. This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix.

The amphiphilic compounds which can be used according to the invention comprise polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol$^{(R)}$).

The lipophilic matrix consists of substances selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerides, the polyethoxylated derivatives thereof, waxes, ceramides, cholesterol derivatives or mixtures thereof having a melting point within the range of 40 to 90° C., preferably from 60 to 70° C.

If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside.

According to an embodiment of the invention, an amphiphilic matrix with high content in active ingredient, typically from 5 to 95% w/w, is first prepared by dispersing the active ingredient or the mixture of active ingredients in a mixture of amphiphilic compounds, such as lecithin, other type II polar lipids, surfactants, or in diethylene glycol monoethyl ether; the resulting amphiphilic matrix is then mixed or kneaded, usually while hot, with lipophilic compounds suitable to form an inert matrix, such as saturated or unsaturated fatty acids, such as palmitic, stearic, myristic, lauric, laurylic, or oleic acids or mixtures thereof with other fatty acids with shorter chain, or salts or alcohols or derivatives of the cited fatty acids, such as mono-, di-, or triglycerides or esters with polyethylene glycols, alone or in combination with waxes, ceramides, cholesterol derivatives or other apolar lipids in various ratios so that the melting or softening points of the lipophilic compounds mixtures is within the range of 40 to 90° C., preferably from 60 to 70° C.

Alternatively, the order of formation of the inert and amphiphilic matrices can be reversed, incorporating the inert matrix inside the amphiphilic compounds.

The resulting inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture.

The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which when passing from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

Examples of hydrogels which can be used according to the invention are compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

In case of taste-masking formulations, the use of polyalcohols such as xylitol, maltitol and mannitol as hydrophilic compounds can also be advantageous.

The lipophilic matrix granules containing the active ingredient are mixed with the hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:50 (lipophilic matrix: hydrophilic matrix). Part of the active ingredient can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitablets.

The compression of the mixture of lipophilic and/or amphiphilic matrix, hydrogel-forming compound and, optionally, active ingredient not inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix. A similar result can also be obtained by coating the lipophilic matrix granules with a hydrophilic polymer coating.

The tablets obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of, for example, methacrylic acids polymers (Eudra or cellulose derivatives, such as cellulose acetophthalate.

Active ingredients which can conveniently be formulated according to the invention comprise:

- analgesics, such as acetaminophen, phenacetin, sodium salicylate;

- antitussives, such as dextromethorphan, codeine phosphate;
- bronchodilators, such as albuterol, procaterol;
- antipsychotics, such as haloperidol, chlorpromazine;
- antihypertensives and coronary-dilators, such as isosorbide mono- and dinitrate, captopril;
- selective β 2 antagonists such as salbutamol, terbutaline, ephedrine, orciprenaline sulfate;
- calcium antagonists, such as nifedipine, nicardipine, diltiazem, verapamil;
- antiparkinson drugs, such as pergolide, carpidopa, levodopa;
- non steroid anti-inflammatory drugs, such as ketoprofen, ibuprofen, diclofenac, diflunisal, piroxicam, naproxen, ketorolac, nimesulide, thiaprophenic acid, mesalazine (5-aminosalicylic acid);
- antihistamines, such as terfenedine, loratadine;
- antidiarrheals and intestinal antiinflammatories, such as loperamide, 5-aminosalicylic, olsalazine, sulfasalazine, budenoside;
- spasmolytics such as octylonium bromide;
- anxiolytics, such as chlordiazepoxide, oxazepam, medazepam, alprazolam, donazepam, lorazepan;
- oral antidiabetics, such as glipizide, metformin, phenformin, gilclazide, glibenclamide;
- cathartics, such as bisacodil, sodium picosulfate;
- antiepileptics, such as valproate, carbamazepine, phenyloin, gabapentin;
- antitumorals, such as flutamide, etoposide;
- oral cavity disinfectants or antimicrobials, such as benzalkonium chloride, cetylpyridinium chloride or tibezonium iodide, and some amino derivatives such as benzydamine and chlorhexidine as well as the salts and derivatives thereof;
- sodium fluoride.

The compositions of the invention can further contain conventional excipients, for example bioadhesive excipients such as chitosans, polyacrylamides, natural or synthetic gums, acrylic acid polymers.

The compositions of the invention can contain more than one active ingredient, each of them being optionally contained in the hydrophilic matrix or in the inert amphiphilic matrix, and are preferably in the form of tablets, capsules or minitablets.

In terms of dissolution characteristics, contact with water or aqueous fluids causes the immediate penetration of water inside the more superficial layer of the matrix which, thanks to the presence of the aqueous solvent, swells due to the distension of the polymeric chains of the hydrogels, giving rise to a high viscosity hydrated front which prevents the further penetration of the solvent itself linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness, until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of inert matrix granules, however induces the diffusion mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient.

The presence of the amphiphilic matrix inside the lipophilic matrix inert allows to prevent any unevenness of the release profile of the active ingredient. The surfactants present in the amphiphilic portion promote wettability of the porous canaliculuses which cross the inert matrix preventing or reducing resistance to penetration of the solvent inside the inert matrix.

To obtain taste masking tablets, the components of the hydrophilic matrix are carefully selected to minimize the active substance release time through penetration accelerated by the canalization induced by the hydrophilic compound.

The following Examples illustrate the invention in greater detail.

EXAMPLE 1

500 g of 5-aminosalicylic-acid and 20 g of octylonium bromide are mixed with 10 g of soy lecithin dissolved in 50 g of a water:ethyl alcohol 1:3 mixture at about 50° C. After homogenization and drying, the granules of the resulting matrix are treated in a kneader with 20 g of carnauba wax and 50 g of stearic acid, heating until homogeneous dispersion, then cold-extruded into small granules. The inert matrix granules are loaded into a mixer in which 30 g of carbopol 971 P and 65 g of hydroxypropyl methylcellulose "are sequentially added." After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 760 mg/tablet. The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 30%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

EXAMPLE 2

50 g of diethylene glycol monoethyl ether are homogeneously distributed on 500 g of microcrystalline cellulose; then 100 g of Budesonide are added, mixing to complete homogenization. This mix is further added with 400 g of Budesonide, then dispersed in a blender containing 100 g of carnauba wax and 100 g of stearic acid preheated at a temperature of 60° C. After kneading for 5 minutes, the mixture is cooled to room temperature and extruded in granules of size below 1 mm.

A suitable mixer is loaded with the matrix granules prepared as above and the following amounts of hydrophilic excipients: 1500 g of hydroxypropyl methylcellulose and 500 g of policarbophil.

The components are mixed until homogeneous dispersion of the matrices, then added with 2450 g of microcrystalline cellulose, 400 g of lactose, 100 g of colloidal silica and 50 g of magnesium stearate. After further 5 minute mixing, the mix is tabletted to unitary weight of 250 mg/tablet.

EXAMPLE 3

850 g of metformin are dispersed in a granulator/kneader with 35 g of diethylene glycol monoethyl ether previously melted with 100 g of stearic acid and 55 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 1040 g of formulation are added with 110 g of hydroxypropyl methylcellulose and 20 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 1170 mg/tablet equivalent to 850 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 35%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

EXAMPLE 4

120 g of octylonium bromide are dispersed in a granulator/kneader with 30 g of stearic acid and 15 g of beeswax in which 10 g of diethylene glycol monoethylene had previously been melted.

The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 10 g of formulation are added with 5 g of hydroxypropyl methylcellulose and 5 g of policarbophyl, 2 g of magnesium stearate and 3 g of microcrystalline cellulose.

The final mixture is tabletted to unitary weight of 200 mg/tablet equivalent to 120 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 25%; after 180 minutes no more than 50%; after 5 hours no more than 70%.

EXAMPLE 5

12 g of diethylene glycol monoethyl ether are loaded on 6 g of microcrystalline cellulose and 6 grams of calcium carbonate, then 100 g of Gabapentin are added and the mixture is homogenized. After that, 800 g of Gabapentin are added which are dispersed in a granulator/kneader with 4.5 g of white wax and 5 g of stearic acid. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 916.5 g of formulation are added with 39.5 g of hydroxypropyl methylcellulose, 10 g of alginic acid, 11 g of magnesium stearate and 6 g of syloid. The final mixture is tabletted to unitary weight of 1000 mg/tablet equivalent to 900 mg of active ingredient.

EXAMPLE 6

50 g (25 g) of carbidopa and 200 g (100 g) of levodopa are dispersed in a granulator/kneader with 60 g (30 g) of stearic acid and 30 g (15 g) of yellow wax, in which 10 (5) g of diethylene glycol monoethyl ether had previously been melted.

5. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 340 g (170 g) of formulation are added with 20 g (10 g) of hydroxypropyl methylcellulose, 10 g (5 g) of xantangum, 16 g (8 g) of microcrystalline cellulose, 4 g (2 g) of magnesium stearate.

The final mixture is tabletted to unitary weight of 400 (200) mg/tablet equivalent to 50 (25) mg of carbidopa and 200 (–100) mg di levodopa.

EXAMPLE 7

4 g of Nimesulide are solubilised in 50 g of diethylene glycol monoethyl ether, then 100 g of microcrystalline cellulose are added to obtain a homogeneous mixture.

The resulting mixture is added in a granulator/kneader with 196 g of Nimesulide, 50 g of stearic acid and 25 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert and amphiphilic matrix system.

425 g of the resulting granulate are added with 60 g of hydroxypropyl methylcellulose, 5 g of policarbophil and 10 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 500 mg/tablet equivalent to 200 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 1 hour no more than 25%, after 2 hours no more than 40%, after 4 hours no more than 60%, after 8 hours no more than 90%.

EXAMPLE 8

500 g of propionyl carnitine are dispersed in a granulator/kneader with 90 g of stearic acid and 40 g of carnauba wax, in which 20 g of diethylene glycol monoethyl ether had previously been melted. The system is heated to carry out the granulation of the active ingredient in the inert/amphiphilic matrix. The resulting 650 g of formulation are added with 60 g of hydroxypropyl methylcellulose and 10 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 720 mg/tablet equivalent to 500 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 40%, after 180 minutes no more than 60%, after 4 hours no more than 80%, after 8 hours no more than 90%.

EXAMPLE 9

One kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with 200 g of cetyl alcohol and 25 g of glycerol palmitostearate the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30° C. The resulting inert matrix is added, keeping stirring and kneading during cooling, with 50 g of soy lecithin and 50 g of ethylene glycol monoethyl ether. The granulate is extruded through a metallic screen of suitable size and mixed with 50 g of hydroxypropyl methylcellulose, 1320 kg of maltodextrins, 2 kg of lactose-cellulose mixture, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to unitary weight of about 500 mg, having hardness suitable for being dissolved in the mouth and a pleasant taste.

EXAMPLE 10

Operating as in the preceding example, chewable tablets are prepared replacing dextrin with mannitol and the lactose-cellulose mixture with xylitol. The resulting tablets have pleasant taste and give upon chewing a sensation of freshness enhancing the flavour.

EXAMPLE 11

Operating as described in example 9, but with the following components:

active ingredient: ibuprofen	mg	100
lipophilic/inert matrix component: cetyl alcohol	mg	15
amphiphilic matrix component: soy lecithin	mg	8
hydrophilic matrix components: mannitol	mg	167
maltodextrins	mg	150
methylhydroxypropylcellulose	mg	30
adjuvants: aspartame	mg	15
flavour	mg	5
colloidal silica	mg	5
magnesium stearate	mg	5

500 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the bitter, irritating taste of the active ingredient.

EXAMPLE 12

Operating as described in example 9, but with the following components:

active ingredient: diclofenac sodium	mg	25
lipophilic/inert matrix component: cetyl alcohol	mg	5
glycerol palmitostearate	mg	5
amphiphilic matrix component: soy lecithin	mg	7
hydrophilic matrix components: xylitol	mg	168
maltodextrins	mg	150
hydroxypropylmethylcellulose	mg	20
adjuvants: aspartame	mg	5
flavour	mg	5
colloidal silica	mg	5
magnesium stearate	mg	5

400 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE 13

Operating as described in example 9, but with the following components:

active ingredient: chlorhexidine	mg	2.5
lipophilic/inert matrix component: cetyl alcohol	mg	0.5
glycerol palmitostearate	mg	0.5
amphiphilic matrix component: diethylene glycol monoethyl ether	mg	0.3
hydrophilic matrix components: xylitol	mg	38
maltodextrins	mg	96
hydroxypropyl methylcellulose	mg	10
adjuvants: aspartame	mg	3
flavour	mg	5
colloidal silica	mg	2
magnesium stearate	mg	2

150 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE 14

One Kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with g 125 of cetyl alcohol: the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30° C., then added with g 30 of lecithin. The resulting matrix is then extruded through a metallic screen of suitable size and mixed with 2.415 kg of lactose, 1.0 kg of maltodextrins, 50 g of hydroxypropyl methylcellulose, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to about 500 mg tablets, having hardness suitable for being dissolved in the mouth and pleasant taste.

The invention claimed is:

1. A controlled release tablet or mini-tablet composition, consisting essentially of:

a hydrophilic first matrix comprising a lipophilic phase and an amphiphilic phase,

wherein said lipophilic phase and said amphiphilic phase are in a second matrix together, and said second matrix is dispersed throughout the hydrophilic first matrix,

wherein said hydrophilic first matrix consists of compounds selected from the group consisting of acrylic or methacrylic acid polymers, acrylic copolymers, methacrylic copolymers, alkyl vinyl polymers, hydroxyalkylcellulose, carboxyalkylcellulose, polysaccharides, dextrins, pectines, starches, starch derivatives, alginic acid, natural gums, synthetic gums, and poylalcohols,

wherein said lipophilic phase is in a granular form and consists of compounds with a melting point between 40 and 90° C. and an active ingredient at least partially incorporated in said lipophilic phase,

wherein said amphiphilic phase comprises an active ingredient at least partially incorporated in said amphiphilic phase.

2. The composition according to claim **1**, further comprising compounds that are polar lipids of type I or II, ceramides, glycol alkyl ethers, esters of fatty acids with polyethylene glycols or diethylene glycols.

3. The composition according to claim **1**, wherein the lipophilic phase comprises one or more compounds selected from the group consisting of unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, mono-, di- or triglycerides of fatty acids, the polyethoxylated derivatives thereof, waxes, and cholesterol derivatives.

4. The composition according to claim **1**, wherein the hydrophilic matrix consists of hydrogel-forming compounds.

5. The composition according to claim **1**, further comprising a gastro-resistant coating.

6. The composition according to claim **5**, wherein the gastro-resistant coating consists of methacrylic acid polymers or cellulose derivatives.

7. The composition according to claim **1**, wherein said composition is in the form of tablets.

8. The composition according to claim **1**, wherein said composition is in the form of minitablets.

9. The composition according to claim **1**, in which the active ingredient belongs to the therapeutical classes of analgesics, antitussives, bronchodilators, antipsychotics, selective β 2 antagonists, calcium antagonists, antiparkinson drugs, non-steroidal anti-inflammatory drugs, antihistamines, antidiarrheals and intestinal antiinflammatories, spasmolytics, anxiolytics, oral anti-diabetics, cathartics, antiepileptics, topical antimicrobials.

10. The composition according to claim **1**, wherein the active ingredient is selected from the group consisting of mesalazine (5-aminosalicylic acid), budesonide, metformin, octylonium bromide, gabapentin, carbidopa, nimesulide, propionylilcarnitine, isosorbide mono- and dinitrate, naproxen, ibuprofen, ketoprofen, diclofenac, thiaprophenic acid, nimesulide, chlorhexidine, benzydamine, tibezonium iodide, cetylpyridinium chloride, benzalkonium chloride, and sodium fluoride.

11. The composition according to claim **1**, further comprising bioadhesive substances.

12. A pharmaceutical composition, comprising the composition according to claim **1**, in the form of tablets chewable or erodible in the buccal cavity or in the first portion of the gastrointestinal tract.

13. The method according to claim **1**, wherein the amphiphilic matrix comprises 5 to 95% by weight of an active ingredient.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,431,943 B1
APPLICATION NO. : 10/009532
DATED : October 7, 2008
INVENTOR(S) : Roberto Villa

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 10, Claim 13, delete “method” and insert --composition-- therefor.

Signed and Sealed this
Sixth Day of December, 2011

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT C

US008293273B2

(12) **United States Patent**
Villa et al.

(10) **Patent No.: US 8,293,273 B2**
(45) **Date of Patent: *Oct. 23, 2012**

(54) **CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(63) Continuation of application No. 13/249,839, filed on Sep. 30, 2011, which is a continuation of application No. 12/210,969, filed on Sep. 15, 2008, now Pat. No. 8,029,823, which is a continuation-in-part of application No. 10/009,532, filed as application No. PCT/EP00/05356 on Jun. 9, 2000, now Pat. No. 7,431,943.

(30) **Foreign Application Priority Data**

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A61K 9/20 (2006.01)
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(52) **U.S. Cl.** **424/464**; 424/474; 424/475

(58) **Field of Classification Search** .... None
See application file for complete search history.

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(57) **ABSTRACT**

Controlled release and taste masking compositions containing one or more active principles inglobated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally inglobated or dispersed in hydrophilic matrices. The use of a plurality of systems for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract.

4 Claims, No Drawings

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CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 13/249,839 filed on Sep. 30, 2011; which is a continuation of application Ser. No. 12/210,969 filed on Sep. 15, 2008, now U.S. Pat. No. 8,029,823; which is a continuation-in-part of application Ser. No. 10/009,532 filed on Dec. 12, 2001, now U.S. Pat. No. 7,431,943; which is the 35 U.S.C. 371 national stage of International application PCT/EP00/05356 filed on Jun. 9, 2000; which claimed priority to Italian applications MI2000A000422 and MI99A001317 filed Mar. 3, 2000 and Jun. 14, 1999, respectively. The entire contents of each of the above-identified applications are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

The present invention relates to controlled release and taste masking compositions containing budesonide as active ingredient incorporated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally incorporated or dispersed in hydrophilic matrices. The use of a plurality of systems mechanism for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract, and it also allows the oral administration of active principles having unfavourable taste characteristics or irritating action on the mucosae of the administration site, particularly in the buccal or gastric area.

The compositions of the invention are suitable to the oral administration or the efficaciously deliver the active ingredient acting topically at some areas of the gastrointestinal tract.

The preparation of a sustained, controlled, delayed, extended or anyhow modified release form can be carried out according to different techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of bioerodible matrices, which are capable of being degraded by the anzimes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Inert matrices, for example, generally entail non-linear, but exponential, release of the active ingredient.

Hydrophilic matrices: have a linear behaviour until a certain fraction of active ingredient has been released, then significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "sire-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-

1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated

The same notion of canalization of an inert matrix is described in U.S. Pat. No. 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials. EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form. The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533, (1998) which improves the application through an annealing technique of the inert polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises: —dissolution of the active ingredient with gastro resistant hydrophilic polymers in organic solvents; —drying of said suspension; —subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application. EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid. WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of the active ingredient. When preparing sustained-, controlled-release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release. Said object has been attained according to the present invention, through the combination of an amphiphilic matrix inside an inert matrix, the latter formulated with a lipophilic polymer in a superficial hydrophilic matrix. The compositions of the invention are characterized by the absence of a first phase in which the medicament superficially present on the matrix is quickly solubilized, and by the fact the amphiphilic layer compensate the lack of affinity of the aqueous solvent with the lipophilic compounds forming the inner inert matrix.

DISCLOSURE OF THE INVENTION

The invention provides controlled release and taste masking oral pharmaceutical compositions containing as active ingredient budesonide comprising:

a) a matrix consisting of lipophilic compounds with melting point lower than 90° C. and optionally by amphiphilic compounds in which the active ingredient is at least partially incorporated;

b) an amphiphilic matrix;
c) an outer hydrophilic matrix in which the lipophilic matrix and the amphiphilic matrix are dispersed;
d) optionally other excipients.

A particular aspect of the invention consists of controlled release oral compositions containing as active ingredient budesonide comprising:
a) a matrix consisting of amphiphilic compounds and lipophilic compounds with melting point below 90° C. in which the active ingredient is at least partially incorporated;
b) an outer hydrophilic matrix in which the lipophilic/amphiphilic matrix is dispersed, preferably by mixing;
c) optionally other excipients.

A further aspect of the invention provides taste masking oral pharmaceutical compositions budesonide containing comprising:
an inert or lipophilic matrix consisting of C6-C20 alcohols or C8-C20 fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six:
an amphiphilic matrix consisting of polar lipids of type I or II or glycols partially etherified with C1-C4 alkyl chains;
an outer hydrophilic matrix containing the above matrices, mainly formed by saccharide, dextrin, polyalcohol or cellulose compounds or by hydrogels or their mixtures;
optional excipients to give stability to the pharmaceutical formulation.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be prepared by a method comprising the following steps:
a) the active ingredient, represented by budesonide, is first inglobated by simple kneading or mixing in a matrix or coating consisting of compounds having amphiphilic properties, which will be further specified below. The active ingredient can be mixed with the amphiphilic compounds without the aid of solvents or with small amounts of water-alcoholic solvents.
b) the matrix obtained as specified under a) is incorporated in a low melting lipophilic excipient or mixture of excipients, if necessary while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion forming an inert matrix which can be reduced in size to obtain inert matrix granules containing the active ingredient particles.
c) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients. The mixture is then subjected to compression or tabletting. This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix. The amphiphilic compounds which can be used according to the invention comprise polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolainine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol®). The lipophilic matrix consists of substances selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerides, the polyethoxylated derivatives thereof, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40 to 90° C., preferably from 60 to 70 C. If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside. An amphiphilic matrix with high content in active ingredient, typically from 5 to 95% w/w, in particular from 20 to 70%, is first prepared by dispersing the active ingredient in a mixture of amphiphilic compounds, such as lecithin, other type II polar lipids, surfactants, or in diethylene glycol monoethyl ether; the resulting amphiphilic matrix is then mixed or kneaded, usually while hot, with lipophilic compounds suitable to form an inert matrix, such as saturated or unsaturated fatty acids, such as palmitic, stearic, myristic, lauric, laurylic, or oleic acids or mixtures thereof with other fatty acids with shorter chain, or salts or alcohols or derivatives of the cited fatty acids, such as mono-, di-, or triglyceride or esters with polyethylene glycols, alone or in combination with waxes, ceramides, cholesterol derivatives or other apolar lipids in various ratios so that the melting or softening points of the lipophilic compounds mixtures is within the range of 40 to 90 C, preferably from 60 to 70 C. Alternatively, the order of formation of the inert and amphiphilic matrices can be reversed, incorporating the inert matrix inside the amphiphilic compounds. The resulting inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture. The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which when passing from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves. Examples of hydrogels which can be used according to the invention are compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid. In case of taste-masking formulations, the use of polyalcohols such as xylitol, maltitol and mannitol as hydrophilic compounds can also be advantageous. The lipophilic matrix granules containing the active ingredient are mixed with the hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:50 (lipophilic matrix: hydrophilic matrix). Part of the active ingredient can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitablets. The compression of the mixture of lipophilic and/or amphiphilic matrix, hydrogel-forming compound and, optionally, active ingredient not inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix. A similar result can also be obtained by coating the lipophilic matrix granules with a hydrophilic polymer coating. The tablets obtainable according to the invention are subjected to known coating processes with a gastro-resistant film, consisting of, for example, acrylic and methacrylic acids polymers (Eudragit®) or copolymer or cellu-

lose derivatives, such as cellulose acetophthalate. The composition of the invention can further contain conventional excipients, for example bioadhesive excipients such as chitosans, polyacrylamides, natural or synthetic gums, acrylic acid polymers.

The compositions of the invention are preferably in the form of tablets, capsules or minitablets. In terms of dissolution characteristics, contact with water or aqueous fluids causes the immediate penetration of water inside the more superficial layer of the matrix which, thanks to the presence of the aqueous solvent, swells due to the distension of the polymeric chains of the hydrogels, giving rise to a high viscosity hydrated front which prevents the further penetration of the solvent itself linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness, until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of inert matrix granules, however induces the diffusion mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient. The presence of the amphiphilic matrix inside the lipophilic matrix inert allows to prevent any unevenness of the release profile of the active ingredient. The surfactants present in the amphiphilic portion promote wettability of the porous canaliculuses which cross the inert matrix preventing or reducing resistance to penetration of the solvent inside the inert matrix. To obtain taste masking tablets, the components of the hydrophilic matrix are carefully selected to minimize the active substance release time through penetration accelerated by the canalization induced by the hydrophilic compound.

EXPERIMENTAL PART

To test the effective ability of the formulations of the invention to modify the release rate and extent of the active ingredient from the dosage form suitable for the drug administration, before any pharmacokinetic study on patients or volunteers, the dissolution test is taken as monitoring and discriminating tool. Dissolution Test Method.

Tablets according to the present invention undergo to dissolution test to verify the formulation capacity in modulating and controlling the rate by which the active ingredient is leaked by the device or dosage form in the environmental medium, generally a buffered solution simulating gastric or intestinal juices.

The dissolution test is performed by introducing individual tablets in a glace vessel containing from 500 to 1000 ml of a buffered solution set to different pH conditions (pH 1, 6.4 and 7.2 are the pH condition generally used in this test applications), so that the whole digestive tract pH conditions, from stomach to large intestine, should be reproduced. To simulate the human body conditions, the test is carried out at a temperature of 37° C.+−<=2° C. and at predetermined time periods samples of the dissolution medium are withdrawn to detect the percentage of active ingredient dissolved over time.

The tablets according to the present invention, when designed to be used to treat inflammatory bowel disease, in principle have to show a good resistance, thanks to the polymeric film resistant to the low pH conditions (intended as <5 to simulate the gastric environment) applied to cover the tablet surface, resistance which last at least for two hours; to target the large intestinal sectors, also the pH condition of 6.4 shown unsuitability to determine a drug leakage from the administration device for a short exposition time and only mediums at pH 7.2 have been able to determine an active ingredient dissolution at a progressive and quite constant rate

during a timeframe from 6 to 12 hours; the dissolution percentage obtained with this tablet formulation were below 15% at first hour sampling, below 25% at second hour sampling, then values were in the range 25% to 55% at fourth hour and a dissolution greater than 80% was achieved at 8^{th} hour sampling.

Example 1

2.7 kg of budesonide, 3.0 kg of lecithin (amphiphilic matrix forming material) and 3.0 kg of stearic acid (lipophilic matrix forming material) are mixing after sieving till an homogeneous mixture is obtained; then add 39.0 kg of inert, functional excipients and 9.0 kg of low viscosity hydroxypropylcellulose (binder) and mix for 10 minutes before adding purified water and kneading to a suitable consistence. Then pass the granulate through a rotating granulator equipped with the suitable screen and transfer the granulate to the fluid bed drier to lower the residual moisture content under 3%.

After a new sieving on the dry, the granulate is added of 9.0 kg of hydroxypropylcellulose (hydrophilic matrix forming material) and the suitable amount of functional excipients (in particular, microcrystalline cellulose, lactose and silicon dioxide) and, after 15 minutes of mixing, magnesium stearate in a suitable quantity to act as lubricant is added.

After a final blending, tablets of around 300 mg of unitary weight are generated.

The core are then subjected to be coated with a suspension obtained introducing into a stainless steel container 5.8 kg of Eudragit™ (methacrylate copolymers), 0.6 kg of triethylcitrate and 3.0 kg of dyes and talc, using alcohol as solvent.

The mean dissolution percentage (as average of six or more tablets) obtained with this tablet formulation were around 10-20% at second hour sampling, in the range 25% to 65% at fourth hour and a dissolution greater than 80% was achieved at 8^{th} hour sampling.

Example 2

Component	mg/tablet
Tablet	
Budesonide	9.0
Stearic Acid	10.0
Lecithin	10.0
Microcristalline cellulose	156.0
Hydroxypropylcellulose	60.0
Lactose monohydrate	50.0
Silicon dioxide	2.0
Magnesium stearate	3.0
Coating materials	
Eudragit L100	14.0
Eudragit S100	12.0
Talc	7.9
Titanium dioxiede	4.5
Triethylcitrate	1.6
Alcohol	q.s.

According to the present invention, coated tablets individually weighing about 220 mg are obtained.

The above described dissolution test is performed on the tablets of Example 2.

The results are the following (indicated as average value):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	15%
after 4 hours at pH 7.2	37%
after 8 hours at pH 7.2	91%

Example 3

Budesonide (3.0 kg) is mixed with soybean Lecithin (5.0 kg) till an homogeneous mixture is obtained. Then carnauba wax (2.0 kg) and stearic acid (2.0 kg) sieved through a fine screen are added. After mixing, the powders are added with other functional excipients and kneaded with a binder solution obtained by dissolving medium viscosity polyvinylpirrolidone in water. After drying in a fluid bed and milling throughout a suitable screen, hydroxypropylmethylcellulose (35.0 kg) and other excipients, including magnesium stearate as lubricant, in a suitable quantity are added and the mixture is blended till an homogeneous powder dispersion is obtained.

The powder mixture is subjected to compression in a rotating tabletting machine and the tablets so obtained are coated in a pan coat with a gastroresistant composition containing Eudragit™, plasticizers, dyes and pigments.

According to the present example, coated tablets individually weighing around 105 mg are obtained.

The results of the above described dissolution test are the following (indicated as average value of at least six tablets):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	9%
after 4 hours at pH 7.2	28%
after 8 hours at pH 7.2	86%

Example 4

50 g of diethylene glycol monoethyl ether are homogeneously distributed on 500 g of microcrystalline cellulose; then 100 g of Budesonide are added, mixing to complete homogenization. This mix is further added with 400 g of Budesonide, then dispersed in a blender containing 100 g of carnauba wax and 100 g of stearic acid preheated at a temperature of 60 [deg.] C. After kneading for 5 minutes, the mixture is cooled to room temperature and extruded in granules of size below 1 mm. A suitable mixer is loaded with the matrix granules prepared as above and the following amounts of hydrophilic excipients: 1500 g of hydroxypropyl methylcellulose and 500 g of Policarbophil™ are added. The components are mixed until homogeneous dispersion of the matrices, then added with 2450 g of microcrystalline cellulose, 400 g of lactose, 100 g of colloidal silica and 50 g of magnesium stearate. After further 5 minute mixing, the mix is tabletted to unitary weight of 250 mg/tablet.

Tablets are then subjected to coating using a suspension n containing polyacrylate and poly methacrilate copolymers in addition to other dyes, plasticizers and colouring agents in solvent (ethylic alcohol).

The results of the dissolution test performed on these coated tablets are the following (indicated as average value of at least six tablets):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	11%
after 4 hours at pH 7.2	32%
after 8 hours at pH 7.2	76%

Example A

500 g of 5-aminosalicylic-acid and 20 g of octylonium bromide are mixed with 10 g of soy lecithin dissolved in 50 g of a water:ethyl alcohol 1:3 mixture at about 50° C. After homogenization and drying, the granules of the resulting matrix are treated in a kneader with 20 g of carnauba wax and 50 g of stearic acid, heating until homogeneous dispersion, then cold-extruded into small granules. The inert matrix granules are loaded into a mixer in which 30 g of carbopol 971 P and 65 g of hydroxypropyl methylcellulose "are sequentially added." After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 760 mg/tablet. The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 30%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

Example B

50 g of diethylene glycol monoethyl ether are homogeneously distributed on 500 g of microcrystalline cellulose; then 100 g of Budesonide are added, mixing to complete homogenization. This mix is further added with 400 g of Budesonide, then dispersed in a blender containing 100 g of carnauba wax and 100 g of stearic acid preheated at a temperature of 60° C. After kneading for 5 minutes, the mixture is cooled to room temperature and extruded in granules of size below 1 mm.

A suitable mixer is loaded with the matrix granules prepared as above and the following amounts of hydrophilic excipients: 1500 g of hydroxypropyl methylcellulose and 500 g of policarbophil.

The components are mixed until homogeneous dispersion of the matrices, then added with 2450 g of microcrystalline cellulose, 400 g of lactose, 100 g of colloidal silica and 50 g of magnesium stearate. After further 5 minute mixing, the mix is tabletted to unitary weight of 250 mg/tablet.

Example C

850 g of metformin are dispersed in a granulator/kneader with 35 g of diethylene glycol monoethyl ether previously melted with 100 g of stearic acid and 55 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 1040 g of formulation are added with 110 g of hydroxypropyl methylcellulose and 20 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 1170 mg/tablet equivalent to 850 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active

principles having the following profile: after 60 minutes no more than 35%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

Example D

120 g of octylonium bromide are dispersed in a granulator/kneader with 30 g of stearic acid and 15 g of beeswax in which 10 g of diethylene glycol monoethylene had previously been melted.

The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 10 g of formulation are added with 5 g of hydroxypropyl methylcellulose and 5 g of policarbophyl, 2 g of magnesium stearate and 3 g of microcrystalline cellulose.

The final mixture is tabletted to unitary weight of 200 mg/tablet equivalent to 120 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 25%; after 180 minutes no more than 50%; after 5 hours no more than 70%.

Example E

12 g of diethylene glycol monoethyl ether are loaded on 6 g of microcrystalline cellulose and 6 grams of calcium carbonate, then 100 g of Gabapentin are added and the mixture is homogenized. After that, 800 g of Gabapentin are added which are dispersed in a granulator/kneader with 4.5 g of white wax and 5 g of stearic acid. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 916.5 g of formulation are added with 39.5 g of hydroxypropyl methylcellulose, 10 g of alginic acid, 11 g of magnesium stearate and 6 g of syloid. The final mixture is tabletted to unitary weight of 1000 mg/tablet equivalent to 900 mg of active ingredient.

Example F

50 g (25 g) of carbidopa and 200 g (100 g) of levodopa are dispersed in a granulator/kneader with 60 g (30 g) of stearic acid and 30 g (15 g) of yellow wax, in which 10 (5) g of diethylene glycol monoethyl ether had previously been melted.

The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 340 g (170 g) of formulation are added with 20 g (10 g) of hydroxypropyl methylcellulose, 10 g (5 g) of xantangum, 16 g (8 g) of microcrystalline cellulose, 4 g (2 g) of magnesium stearate.

The final mixture is tabletted to unitary weight of 400 (200) mg/tablet equivalent to 50 (25) mg of carbidopa and 200 (−100) mg di levodopa.

Example G

4 g of Nimesulide are solubilised in 50 g of diethylene glycol monoethyl ether, then 100 g of microcrystalline cellulose are added to obtain a homogeneous mixture.

The resulting mixture is added in a granulator/kneader with 196 g of Nimesulide, 50 g of stearic acid and 25 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert and amphiphilic matrix system.

425 g of the resulting granulate are added with 60 g of hydroxypropyl methylcellulose, 5 g of policarbophil and 10 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 500 mg/tablet equivalent to 200 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 1 hour no more than 25%, after 2 hours no more than 40%, after 4 hours no more than 60%, after 8 hours no more than 90%.

Example H

500 g of propionyl carnitine are dispersed in a granulator/kneader with 90 g of stearic acid and 40 g of carnauba wax, in which 20 g of diethylene glycol monoethyl ether had previously been melted. The system is heated to carry out the granulation of the active ingredient in the inert/amphiphilic matrix. The resulting 650 g of formulation are added with 60 g of hydroxypropyl methylcellulose and 10 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 720 mg/tablet equivalent to 500 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 40%, after 180 minutes no more than 60%, after 4 hours no more than 80%, after 8 hours no more than 90%.

Example I

One kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with 200 g of cetyl alcohol and 25 g of glycerol palmitostearate the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30° C. The resulting inert matrix is added, keeping stirring and kneading during cooling, with 50 g of soy lecithin and 50 g of ethylene glycol monoethyl ether. The granulate is extruded through a metallic screen of suitable size and mixed with 50 g of hydroxypropyl methylcellulose, 1320 kg of maltodextrins, 2 kg of lactose-cellulose mixture, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to unitary weight of about 500 mg, having hardness suitable for being dissolved in the mouth and a pleasant taste.

Example J

Operating as in the preceding Example, chewable tablets are prepared replacing dextrin with mannitol and the lactose-cellulose mixture with xylitol. The resulting tablets have pleasant taste and give upon chewing a sensation of freshness enhancing the flavour.

Example K

Operating as described in Example I, but with the following components:

active ingredient: ibuprofen	mg	100
lipophilic/inert matrix component: cetyl alcohol	mg	15
amphiphilic matrix component: soy lecithin	mg	8
hydrophilic matrix components: mannitol	mg	167
maltodextrins	mg	150
methylhydroxypropylcellulose	mg	30
adjuvants: aspartame	mg	15

-continued

flavour	mg	5
colloidal silica	mg	5
magnesium stearate	mg	5

500 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the bitter, irritating taste of the active ingredient.

Example L

Operating as described in Example I, but with the following components:

active ingredient: diclofenac sodium	mg	25
lipophilic/inert matrix component: cetyl alcohol	mg	5
glycerol palmitostearate	mg	5
amphiphilic matrix component: soy lecithin	mg	7
hydrophilic matrix components: xylitol	mg	168
maltodextrins	mg	150
hydroxypropylmethylcellulose	mg	20
adjuvants: aspartame	mg	5
flavour	mg	5
colloidal silica	mg	5
magnesium stearate	mg	5

400 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

Example M

Operating as described in Example I, but with the following components:

active ingredient: chlorhexidine	mg	2.5
lipophilic/inert matrix component: cetyl alcohol	mg	0.5
glycerol palmitostearate	mg	0.5
amphiphilic matrix component: diethylene glycol monoethyl ether	mg	0.3
hydrophilic matrix components: xylitol	mg	38

-continued

maltodextrins	mg	96
hydroxypropyl methylcellulose	mg	10
adjuvants: aspartame	mg	3
flavour	mg	5
colloidal silica	mg	2
magnesium stearate	mg	2

150 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

Example N

One Kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with g 125 of cetyl alcohol: the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30° C., then added with g 30 of lecithin. The resulting matrix is then extruded through a metallic screen of suitable size and mixed with 2.415 kg of lactose, 1.0 kg of maltodextrins, 50 g of hydroxypropyl methylcellulose, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to about 500 mg tablets, having hardness suitable for being dissolved in the mouth and pleasant taste.

The invention claimed is:

1. A controlled release oral pharmaceutical composition comprising:

(1) a tablet core comprising:

a) budesonide in an amount effective for treatment of inflammatory bowel disease in the gastrointestinal tract,

b) stearic acid;

c) lecithin; and

d) hydroxypropyl cellulose; and

(2) a gastro-resistant coating on said tablet core, said coating comprising at least one methacrylic acid polymer.

2. The composition of claim **1**, wherein said tablet core further comprises microcrystalline cellulose, lactose, and magnesium stearate.

3. The composition of claim **1**, comprising 9 mg of budesonide.

4. The composition of claim **2**, comprising 9 mg of budesonide.

* * * * *

EXHIBIT D

US008784888B2

(12) **United States Patent**
Villa et al.

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(45) **Date of Patent: *Jul. 22, 2014**

(54) **CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION**

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This patent is subject to a terminal disclaimer.

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(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Controlled release and taste masking compositions containing one or more active principles inglobated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally inglobated or dispersed in hydrophilic matrices. The use of a plurality of systems for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract.

9 Claims, No Drawings

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CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 13/462,409 filed on May 2, 2012, now U.S. Pat. No. 8,293,273; which is a continuation of Ser. No. 13/249,839 filed on Sep. 30, 2011; which is a continuation of application Ser. No. 12/210,969 filed on Sep. 15, 2008, which reissued as U.S. Pat. No. RE43,799 from U.S. Pat. No. 8,029,823; which is a continuation-in-part of application Ser. No. 10/009,532 filed on Dec. 12, 2001, now U.S. Pat. No. 7,431,943; which is the 35 U.S.C. 371 national stage of International application PCT/EP00/05356 filed on Jun. 9, 2000; which claimed priority to Italian applications MI2000A000422 and MI99A001317 filed Mar. 3, 2000 and Jun. 14, 1999, respectively. The entire contents of each of the above-identified applications are hereby incorporated by reference.

The present invention relates to controlled release and taste-masking compositions containing one or more active principles incorporated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally incorporated or dispersed in hydrophilic matrices. The use of a plurality of systems for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract, and it also allows the oral administration of active principles having unfavourable taste characteristics or irritating action on the mucosae of the administration site, particularly in the buccal area.

The compositions of the invention can contain active principles belonging to the therapeutical classes of analgesics, antiinflammatories, cardioactives, tranquillizers, antihypertensives, disinfectants and topical antimicrobials, antiparkinson drugs, antihistamines and are suitable to the oral administration or for acting topically at some areas of the gastrointestinal tract.

TECHNOLOGICAL BACKGROUND

The preparation of a sustained, controlled, delayed or anyhow modified release form can be carried out according to different known techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of bioerodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Inert matrices, for example, generally entail non-linear, but exponential, release of the active ingredient.

Hydrophilic matrices have a linear behaviour until a certain fraction of active ingredient has been released; then they significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "site-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated.

The same notion of canalization of an inert matrix is described in U.S. Pat. No. 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials.

EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form.

The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533, (1998) which improves the application through an annealing technique of the inert polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises:

- dissolution of the active ingredient with gastro-resistant hydrophilic polymers in organic solvents;
- drying of said suspension;
- subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application.

EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid.

WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of the active ingredient.

When preparing sustained-, controlled-release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release.

Said object has been attained according to the present invention, through the combination of an amphiphilic matrix inside an inert matrix, the latter formulated with a lipophilic polymer in a superficial hydrophilic matrix. The compositions of the invention are characterized by the absence of a first phase in which the medicament superficially present on

the matrix is quickly solubilized, and by the fact the amphiphilic layer compensate the lack of affinity of the aqueous solvent with the lipophilic compounds forming the inner inert matrix.

DISCLOSURE OF THE INVENTION

The invention provides controlled release and taste masking oral pharmaceutical compositions containing an active ingredient, comprising:

a) a matrix consisting of lipophilic compounds with melting point lower than 90° C. and optionally by amphiphilic compounds in which the active ingredient is at least partially incorporated;

b) optionally an amphiphilic matrix;

c) an outer hydrophilic matrix in which the lipophilic matrix and the optional amphiphilic matrix are dispersed;

d) optionally other excipients.

A particular aspect of the invention consists of controlled release oral compositions containing one or more active ingredients comprising:

a) a matrix consisting of amphiphilic compounds and lipophilic compounds with melting point below 90° C. in which the active ingredient is at least partially incorporated;

b) an outer hydrophilic matrix in which the lipophilic/amphiphilic matrix is dispersed;

c) optional other excipients.

A further aspect of the invention provides taste masking oral pharmaceutical compositions containing one or more active ingredients comprising:

- an inert or lipophilic matrix consisting of C6-C20-alcohols or C8-C20 fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six;
- an amphiphilic matrix consisting of polar lipids of type I or II or glycols partially etherified with C1-C4 alkyl chains;
- an outer hydrophilic matrix containing the above matrices, mainly formed by saccharide, dextrin, polyalcohol or cellulose compounds or by hydrogels;
- optional excipients to give stability to the pharmaceutical formulation.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be prepared by a method comprising the following steps:

a) the active ingredient is first inglobated by simple kneading or mixing in a matrix or coating consisting of compounds having amphiphilic properties, which will be further specified below. The active principle(s) can be mixed with the amphiphilic compounds without the aid of solvents or with small amounts of water-alcoholic solvents.

b) The matrix obtained in a) is incorporated in a low melting lipophilic excipient or mixture of excipients, while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion. After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain inert matrix granules containing the active ingredient particles.

c) The inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients. The mixture is then subjected to compression or tabletting. This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix.

The amphiphilic compounds which can be used according to the invention comprise polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol$^{(R)}$).

The lipophilic matrix consists of substances selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerides, the polyethoxylated derivatives thereof, waxes, ceramides, cholesterol derivatives or mixtures thereof having a melting point within the range of 40 to 90° C., preferably from 60 to 70° C.

If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside.

According to an embodiment of the invention, an amphiphilic matrix with high content in active ingredient, typically from 5 to 95% w/w, is first prepared by dispersing the active ingredient or the mixture of active ingredients in a mixture of amphiphilic compounds, such as lecithin, other type II polar lipids, surfactants, or in diethylene glycol monoethyl ether; the resulting amphiphilic matrix is then mixed or kneaded, usually while hot, with lipophilic compounds suitable to form an inert matrix, such as saturated or unsaturated fatty acids, such as palmitic, stearic, myristic, lauric, laurylic, or oleic acids or mixtures thereof with other fatty acids with shorter chain, or salts or alcohols or derivatives of the cited fatty acids, such as mono-, di-, or triglycerides or esters with polyethylene glycols, alone or in combination with waxes, ceramides, cholesterol derivatives or other apolar lipids in various ratios so that the melting or softening points of the lipophilic compounds mixtures is within the range of 40 to 90° C., preferably from 60 to 70° C.

Alternatively, the order of formation of the inert and amphiphilic matrices can be reversed, incorporating the inert matrix inside the amphiphilic compounds.

The resulting inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture.

The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which when passing from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

Examples of hydrogels which can be used according to the invention are compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

In case of taste-masking formulations, the use of polyalcohols such as xylitol, maltitol and mannitol as hydrophilic compounds can also be advantageous.

The lipophilic matrix granules containing the active ingredient are mixed with the hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:50 (lipophilic matrix: hydrophilic matrix). Part of the active ingredient can optionally be mixed with hydrophilic sub-

stances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitablets.

The compression of the mixture of lipophilic and/or amphiphilic matrix, hydrogel-forming compound and, optionally, active ingredient not inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix. A similar result can also be obtained by coating the lipophilic matrix granules with a hydrophilic polymer coating.

The tablets obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of, for example, methacrylic acids polymers (Eudragit$^{(R)}$) or cellulose derivatives, such as cellulose acetophthalate.

Active ingredients which can conveniently be formulated according to the invention comprise:

analgesics, such as acetaminophen, phenacetin, sodium salicylate; antitussives, such as dextromethorphan, codeine phosphate;

bronchodilators, such as albuterol, procaterol;

antipsychotics, such as haloperidol, chlorpromazine;

antihypertensives and coronary-dilators, such as isosorbide mono- and dinitrate, captopril;

selective β 2 antagonists such as salbutamol, terbutaline, ephedrine, orciprenaline sulfate;

calcium antagonists, such as nifedipine, nicardipine, diltiazem, verapamil;

antiparkinson drugs, such as pergolide, carpidopa, levodopa;

non steroid anti-inflammatory drugs, such as ketoprofen, ibuprofen, diclofenac, diflunisal, piroxicam, naproxen, ketorolac, nimesulide, thiaprophenic acid, mesalazine (5-aminosalicylic acid); antihistamines, such as terfenedine, loratadine;

antidiarrheals and intestinal antiinflammatories, such as loperamide, 5-aminosalicylic, olsalazine, sulfasalazine, budenoside;

spasmolytics such as octylonium bromide;

anxiolytics, such as chlordiazepoxide, oxazepam, medazepam, alprazolam, donazepam, lorazepan;

oral antidiabetics, such as glipizide, metformin, phenformin, gilclazide, glibenclamide;

cathartics, such as bisacodil, sodium picosulfate;

antiepileptics, such as valproate, carbamazepine, phenyloin, gabapentin;

antitumorals, such as flutamide, etoposide;

oral cavity disinfectants or antimicrobials, such as benzalkonium chloride, cetylpyridinium chloride or tibezonium iodide, and some amino derivatives such as benzydamine and chlorhexidine as well as the salts and derivatives thereof;

sodium fluoride.

The compositions of the invention can further contain conventional excipients, for example bioadhesive excipients such as chitosans, polyacrylamides, natural or synthetic gums, acrylic acid polymers.

The compositions of the invention can contain more than one active ingredient, each of them being optionally contained in the hydrophilic matrix or in the inert amphiphilic matrix, and are preferably in the form of tablets, capsules or minitablets.

In terms of dissolution characteristics, contact with water or aqueous fluids causes the immediate penetration of water inside the more superficial layer of the matrix which, thanks to the presence of the aqueous solvent, swells due to the distension of the polymeric chains of the hydrogels, giving rise to a high viscosity hydrated front which prevents the further penetration of the solvent itself linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness, until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of inert matrix granules, however induces the diffusion mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient.

The presence of the amphiphilic matrix inside the lipophilic matrix inert allows to prevent any unevenness of the release profile of the active ingredient. The surfactants present in the amphiphilic portion promote wettability of the porous canaliculuses which cross the inert matrix preventing or reducing resistance to penetration of the solvent inside the inert matrix.

To obtain taste masking tablets, the components of the hydrophilic matrix are carefully selected to minimize the active substance release time through penetration accelerated by the canalization induced by the hydrophilic compound.

The following Examples illustrate the invention in greater detail.

EXAMPLE 1

500 g of 5-aminosalicylic-acid and 20 g of octylonium bromide are mixed with 10 g of soy lecithin dissolved in 50 g of a water:ethyl alcohol 1:3 mixture at about 50° C. After homogenization and drying, the granules of the resulting matrix are treated in a kneader with 20 g of carnauba wax and 50 g of stearic acid, heating until homogeneous dispersion, then cold-extruded into small granules. The inert matrix granules are loaded into a mixer in which 30 g of carbopol 971 P and 65 g of hydroxypropyl methylcellulose are sequentially added. After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 760 mg/tablet. The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 30%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

EXAMPLE 2

50 g of diethylene glycol monoethyl ether are homogeneously distributed on 500 g of microcrystalline cellulose; then 100 g of Budesonide are added, mixing to complete homogenization. This mix is further added with 400 g of Budesonide, then dispersed in a blender containing 100 g of carnauba wax and 100 g of stearic acid preheated at a temperature of 60° C. After kneading for 5 minutes, the mixture is cooled to room temperature and extruded in granules of size below 1 mm.

A suitable mixer is loaded with the matrix granules prepared as above and the following amounts of hydrophilic excipients: 1500 g of hydroxypropyl methylcellulose and 500 g of policarbophil.

The components are mixed until homogeneous dispersion of the matrices, then added with 2450 g of microcrystalline cellulose, 400 g of lactose, 100 g of colloidal silica and 50 g

of magnesium stearate. After further 5 minute mixing, the mix is tabletted to unitary weight of 250 mg/tablet.

EXAMPLE 3

850 g of metformin are dispersed in a granulator/kneader with 35 g of diethylene glycol monoethyl ether previously melted with 100 g of stearic acid and 55 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 1040 g of formulation are added with 110 g of hydroxypropyl methylcellulose and 20 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 1170 mg/tablet equivalent to 850 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 35%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

EXAMPLE 4

120 g of octylonium bromide are dispersed in a granulator/kneader with 30 g of stearic acid and 15 g of beeswax in which 10 g of diethylene glycol monoethylene had previously been melted.

The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 10 g of formulation are added with 5 g of hydroxypropyl methylcellulose and 5 g of policarbophyl, 2 g of magnesium stearate and 3 g of microcrystalline cellulose.

The final mixture is tabletted to unitary weight of 200 mg/tablet equivalent to 120 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 25%; after 180 minutes no more than 50%; after 5 hours no more than 70%.

EXAMPLE 5

12 g of diethylene glycol monoethyl ether are loaded on 6 g of microcrystalline cellulose and 6 grams of calcium carbonate, then 100 g of Gabapentin are added and the mixture is homogenized. After that, 800 g of Gabapentin are added which are dispersed in a granulator/kneader with 4.5 g of white wax and 5 g of stearic acid. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 916.5 g of formulation are added with 39.5 g of hydroxypropyl methylcellulose, 10 g of alginic acid, 11 g of magnesium stearate and 6 g of syloid. The final mixture is tabletted to unitary weight of 1000 mg/tablet equivalent to 900 mg of active ingredient.

EXAMPLE 6

50 g (25 g) of carbidopa and 200 g (100 g) of levodopa are dispersed in a granulator/kneader with 60 g (30 g) of stearic acid and 30 g (15 g) of yellow wax, in which 10 (5) g of diethylene glycol monoethyl ether had previously been melted.

The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 340 g (170 g) of formulation are added with 20 g (10 g) of hydroxypropyl methylcellulose, 10 g (5 g) of xantangum, 16 g (8 g) of microcrystalline cellulose, 4 g (2 g) of magnesium stearate.

The final mixture is tabletted to unitary weight of 400 (200) mg/tablet equivalent to 50 (25) mg of carbidopa and 200 (100) mg di levodopa.

EXAMPLE 7

4 g of Nimesulide are solubilised in 50 g of diethylene glycol monoethyl ether, then 100 g of microcrystalline cellulose are added to obtain a homogeneous mixture.

The resulting mixture is added in a granulator/kneader with 196 g of Nimesulide, 50 g of stearic acid and 25 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert and amphiphilic matrix system.

425 g of the resulting granulate are added with 60 g of hydroxypropyl methylcellulose, 5 g of policarbophil and 10 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 500 mg/tablet equivalent to 200 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 1 hour no more than 25%, after 2 hours no more than 40%, after 4 hours no more than 60%, after 8 hours no more than 90%.

EXAMPLE 8

500 g of propionyl carnitine are dispersed in a granulator/kneader with 90 g of stearic acid and 40 g of carnauba wax, in which 20 g of diethylene glycol monoethyl ether had previously been melted. The system is heated to carry out the granulation of the active ingredient in the inert/amphiphilic matrix. The resulting 650 g of formulation are added with 60 g of hydroxypropyl methylcellulose and 10 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 720 mg/tablet equivalent to 500 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 40%, after 180 minutes no more than 60%, after 4 hours no more than 80%, after 8 hours no more than 90%.

EXAMPLE 9

One kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with 200 g of cetyl alcohol and 25 g of glycerol palmitostearate the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30° C. The resulting inert matrix is added, keeping stirring and kneading during cooling, with 50 g of soy lecithin and 50 g of ethylene glycol monoethyl ether. The granulate is extruded through a metallic screen of suitable size and mixed with 50 g of hydroxypropyl methylcellulose, 1320 kg of maltodextrins, 2 kg of lactose-cellulose mixture, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to unitary weight of about 500 mg, having hardness suitable for being dissolved in the mouth and a pleasant taste.

EXAMPLE 10

Operating as in the preceding example, chewable tablets are prepared replacing dextrin with mannitol and the lactose-cellulose mixture with xylitol. The resulting tablets have pleasant taste and give upon chewing a sensation of freshness enhancing the flavour.

EXAMPLE 11

Operating as described in example 9, but with the following components:

active ingredient: ibuprofen	mg	100
lipophilic/inert matrix component: cetyl alcohol	mg	15
amphiphilic matrix component: soy lecithin	mg	8
hydrophilic matrix components: mannitol	mg	167
maltodextrins	mg	150
methylhydroxypropylcellulose	mg	30
adjuvants: aspartame	mg	15
flavor	mg	5
colloidal silica	mg	5
magnesium stearate	mg	5

500 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the bitter, irritating taste of the active ingredient.

EXAMPLE 12

Operating as described in example 9, but with the following components:

active ingredient: diclofenac sodium	mg	25
lipophilic/inert matrix component: cetyl alcohol	mg	5
glycerol palmitostearate	mg	5
amphiphilic matrix component: soy lecithin	mg	7
hydrophilic matrix components: xylitol	mg	168
maltodextrins	mg	150
hydroxypropylmethylcellulose	mg	20
adjuvants: aspartame	mg	5
flavor	mg	5
colloidal silica	mg	5
magnesium stearate	mg	5

400 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE 13

Operating as described in example 9, but with the following components:

active ingredient: chlorhexidine	mg	2.5
lipophilic/inert matrix component: cetyl alcohol	mg	0.5
glycerol palmitostearate	mg	0.5
amphiphilic matrix component: diethylene glycol monoethyl ether	mg	0.3
hydrophilic matrix components: xylitol	mg	38
maltodextrins	mg	96
hydroxypropyl methylcellulose	mg	10
adjuvants: aspartame	mg	3
flavor	mg	5
colloidal silica	mg	2
magnesium stearate	mg	2

150 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE 14

One Kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with g 125 of cetyl alcohol: the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30° C., then added with g 30 of lecithin. The resulting matrix is then extruded through a metallic screen of suitable size and mixed with 2.415 kg of lactose, 1.0 kg of maltodextrins, 50 g of hydroxypropyl methylcellulose, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to about 500 mg tablets, having hardness suitable for being dissolved in the mouth and pleasant taste.

The invention claimed is:

1. A controlled release oral pharmaceutical composition consisting essentially of:

(1) a tablet core consisting essentially of:

a) budesonide in an amount effective to treat intestinal inflammatory disease; and

b) a macroscopically homogeneous composition comprising at least one lipophilic excipient, at least one amphiphilic excipient, and at least one hydrogel-forming hydrophilic excipient other than a gum, wherein said budesonide is dispersed in said macroscopically homogeneous composition; and

(2) a coating on said tablet core, said coating consisting essentially of a gastro-resistant film.

2. A controlled release oral pharmaceutical composition according to claim **1**, wherein said at least one hydrogel-forming hydrophilic excipient comprises at least one hydroxyalkyl cellulose.

3. A controlled release oral pharmaceutical composition according to claim **1**, wherein said gastro-resistant film consists essentially of at least one methacrylic acid polymer.

4. A controlled release oral pharmaceutical composition according to claim **3**, wherein said at least one hydrogel-forming hydrophilic excipient comprises at least one hydroxyalkyl cellulose.

5. A controlled release oral pharmaceutical composition according to claim **1**, wherein said at least one lipophilic excipient comprises stearic acid or magnesium stearate.

6. A controlled release oral pharmaceutical composition according to claim **5**, wherein said at least one hydrogel-forming hydrophilic excipient comprises at least one hydroxyalkyl cellulose.

7. A controlled release oral pharmaceutical composition according to claim **1**, wherein said at least one amphiphilic excipient comprises lecithin.

8. A controlled release oral pharmaceutical composition according to claim **7**, wherein said at least one hydrogel-forming hydrophilic excipient comprises at least one hydroxyalkyl cellulose.

9. A controlled release oral pharmaceutical composition according to claim **7**, wherein said at least one lipophilic excipient comprises stearic acid or magnesium stearate.

* * * * *

EXHIBIT E

US008895064B2

(12) **United States Patent**
Villa et al.

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(45) **Date of Patent: *Nov. 25, 2014**

(54) **CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION**

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None

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(57) **ABSTRACT**

Controlled release and taste masking compositions containing one or more active principles inglobated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally inglobated or dispersed in hydrophilic matrices. The use of a plurality of systems for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract.

12 Claims, No Drawings

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CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION

The present invention relates to controlled release, delayed release, prolonged release, extended release and/or taste masking compositions containing budesonide as active ingredient incorporated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally incorporated or dispersed in hydrophilic matrices. The use of a plurality of systems mechanism for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract, and it also allows the oral administration of active principles having unfavourable taste characteristics or irritating action on the mucosae of the administration site, particularly in the buccal or gastric area.

The compositions of the invention are suitable to the oral administration or the efficaciously deliver the active ingredient acting topically at some areas of the gastrointestinal tract.

TECHNOLOGICAL BACKGROUND

The preparation of a sustained, controlled, delayed, extended or anyhow modified release form can be carried out according to different techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of bioerodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Inert matrices, for example, generally entail non-linear, but exponential, release of the active ingredient.

Hydrophilic matrices: have a linear behaviour until a certain fraction of active ingredient has been released, then significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "sire-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated

The same notion of canalization of an inert matrix is described in U.S. Pat. No. 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials. EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form. The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533, (1998) which improves the application through an annealing technique of the inert polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises:—dissolution of the active ingredient with gastro resistant hydrophilic polymers in organic solvents;—drying of said suspension;—subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application. EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid. WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of the active ingredient. When preparing sustained-, controlled-release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release. Said object has been attained according to the present invention, through the combination of an amphiphilic matrix inside an inert matrix, the latter formulated with a lipophilic polymer in a superficial hydrophilic matrix. The compositions of the invention are characterized by the absence of a first phase in which the medicament superficially present on the matrix is quickly solubilized, and by the fact the amphiphilic layer compensate the lack of affinity of the aqueous solvent with the lipophilic compounds forming the inner inert matrix.

DISCLOSURE OF THE INVENTION

The invention provides controlled release, delayed release, prolonged release, extended release and/or taste masking oral pharmaceutical compositions containing as active ingredient budesonide comprising:

a) a matrix consisting of lipophilic compounds with melting point lower than 90° C. and optionally by amphiphilic compounds in which the active ingredient is at least partially incorporated;

b) an amphiphilic matrix;

c) an outer hydrophilic matrix in which the lipophilic matrix and the amphiphilic matrix are dispersed;

d) optionally other excipients.

A particular aspect of the invention consists of controlled release, delayed release, prolonged release, extended release and/or taste masking oral compositions containing as active ingredient budesonide comprising:

a) a matrix consisting of amphiphilic compounds and lipophilic compounds with melting point below 90° C. in which the active ingredient is at least partially incorporated;
b) an outer hydrophilic matrix in which the lipophilic/amphiphilic matrix is dispersed, preferably by mixing;
c) optionally other excipients.

According to a preferred embodiment of the invention, the active ingredient budesonide is contained in the composition in an amount from 1.5 to 15% w/w, based on the total weight of the composition. According to a preferred embodiment of the invention, budesonide is comprised in an amount from 5 to 10 mgs/dose unit, more preferably in an amount of about 6 mgs/dose unit or 9 mgs/dose unit.

A further aspect of the invention provides taste masking oral pharmaceutical compositions budesonide containing comprising:

an inert or lipophilic matrix consisting of C6-C20 alcohols or C8-C20 fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six:

an amphiphilic matrix consisting of polar lipids of type I or II or glycols partially etherified with C1-C4 alkyl chains;

an outer hydrophilic matrix containing the above matrices, mainly formed by saccharide, dextrin, polyalcohol or cellulose compounds or by hydrogels or their mixtures;

optional excipients to give stability to the pharmaceutical formulation.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be prepared by a method comprising the following steps:

a) the active ingredient, represented by budesonide, is first inglobated by simple kneading or mixing in a matrix or coating consisting of compounds having amphiphilic properties, which will be further specified below. The active ingredient can be mixed with the amphiphilic compounds without the aid of solvents or with small amounts of water-alcoholic solvents.
b) the matrix obtained as specified under a) is incorporated in a low melting lipophilic excipient or mixture of excipients, if necessary while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion. forming an inert matrix which can be reduced in size to obtain inert matrix granules containing the active ingredient particles.
c) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients. The mixture is then subjected to compression or tabletting. This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix. The amphiphilic compounds which can be used according to the invention comprise polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol^{R}). The lipophilic matrix consists of substances selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerids, the polyethoxylated derivatives thereof, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40 to 90 C., preferably from 60 to 70 C. If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside. An amphiphilic matrix with high content in active ingredient, typically from 5 to 95% w/w, in particular from 20 to 70%, or from 1.5 to 15% w/w, is first prepared by dispersing the active ingredient in a mixture of amphiphilic compounds, such as lecithin, other type II polar lipids, surfactants, or in diethylene glycol monoethyl ether; the resulting amphiphilic matrix is then mixed or kneaded, usually while hot, with lipophilic compounds suitable to form an inert matrix, such as saturated or unsaturated fatty acids, such as palmitic, stearic, myristic, lauric, laurylic, or oleic acids or mixtures thereof with other fatty acids with shorter chain, or salts or alcohols or derivatives of the cited fatty acids, such as mono-, di-, or triglycerids or esters with polyethylene glycols, alone or in combination with waxes, ceramides, cholesterol derivatives or other apolar lipids in various ratios so that the melting or softening points of the lipophilic compounds mixtures is within the range of 40 to 90° C., preferably from 60 to 70° C. Alternatively, the order of formation of the inert and amphiphilic matrices can be reversed, incorporating the inert matrix inside the amphiphilic compounds. The resulting inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture. The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which when passing from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves. Examples of hydrogels which can be used according to the invention are compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid. In case of taste-masking formulations, the use of polyalcohols such as xylitol, maltitol and mannitol as hydrophilic compounds can also be advantageous. The lipophilic matrix granules containing the active ingredient are mixed with the hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:50 (lipophilic matrix: hydrophilic matrix). Part of the active ingredient can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitablets. The compression of the mixture of lipophilic and/or amphiphilic matrix, hydrogel-forming compound and, optionally, active ingredient not inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix. A similar result can also be obtained by coating

the lipophilic matrix granules with a hydrophilic polymer coating. The tablets obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film/gastro-resistant coating, consisting of, for example, acrylic and/or methacrylic acids polymers (Eudragit (R)) or copolymers (Eudragit S/L) or cellulose derivatives, such as cellulose acetophthalate/s.

According to a preferred embodiment of invention the gastro-protective coating can be represented by a mixture of acrylic and/or methacrylic acid copolymers type A and/or type B (as, for example, Eudragit S100 and/or Eudragit L100).

According to a further embodiment of the invention, the mixture of acrylic and/or methacrylic acid copolymers type A and/or type B is preferably in a range ratio from 1:5 to 5:1.

According to another further embodiment, the gastro-protective coating also optionally comprises plasticizers, dyes, at least one water-solvent, at least one organic solvent or a mixture thereof.

The composition of the invention can further contain conventional excipients, for example bioadhesive excipients such as chitosans, polyacrylamides, natural or synthetic gums, acrylic acid polymers. The compositions of the invention are preferably in the form of tablets, capsules or minitablets. In terms of dissolution characteristics, contact with water or aqueous fluids causes the immediate penetration of water inside the more superficial layer of the matrix which, thanks to the presence of the aqueous solvent, swells due to the distension of the polymeric chains of the hydrogels, giving rise to a high viscosity hydrated front which prevents the further penetration of the solvent itself linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness, until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of inert matrix granules, however induces the diffusion mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient. The presence of the amphiphilic matrix inside the lipophilic matrix inert allows to prevent any unevenness of the release profile of the active ingredient. The surfactants present in the amphiphilic portion promote wettability of the porous canaliculuses which cross the inert matrix preventing or reducing resistance to penetration of the solvent inside the inert matrix. To obtain taste masking tablets, the components of the hydrophilic matrix are carefully selected to minimize the active substance release time through penetration accelerated by the canalization induced by the hydrophilic compound.

The compositions of the present invention are preferably intended for use in the treatment of subjects suffering from Inflammatory Bowel Disease and/or Irritable Bowel Syndrome. Preferably, according to the invention Inflammatory Bowel Disease is Crohn's disease and Irritable Bowel Syndrome is Ulcerative Colitis.

Further object of the invention is then a method for the treatment of a subject suffering from Inflammatory Bowel Disease and/or Irritable Bowel Syndrome comprising administering a pharmaceutical composition comprising an effective amount of budesonide, as above defined and disclosed, to a subject in need of such treatment. Preferably, according to the invention Inflammatory Bowel Disease is Crohn's disease and Irritable Bowel Syndrome is Ulcerative Colitis.

According to a preferred embodiment of the invention the budesonide composition release is:

below 15% within the first hour at pH 7.2,
greater than 80% within eight hours at pH 7.2.

According to a further preferred embodiment of the invention the budesonide composition release is:

below 15% within the first hour at pH 7.2,
below 25% within two hours at pH 7.2;
between 25% and 55% within four hours pH 7.2;
greater than 80% within eight hours at pH 7.2

According to a further preferred embodiment of the invention the budesonide composition release is:

below 15% with the first hour at pH 7.2,
between 20% and 60% within four hours at ph 7.2;
greater than 80% at eight hour at pH 7.2

Experimental Part

To test the effective ability of the formulations of the invention to modify the release rate and extent of the active ingredient from the dosage form suitable for the drug administration, before any pharmacokinetic study on patients or volunteers, the dissolution test is taken as monitoring and discriminating tool (according to USP type II apparatus complying with USP <711>).

Also the bioavailability profile of the formulations of the invention is carried out, in comparison with a the marked formulation Entocort® EC 3×3 mg capsules. As preferred embodiment, the bioavailability study showed a T_{max} average value higher than 8 hours and a MRT average value higher than 14 hours.

According to the invention, T_{max} corresponds to "time to peak concentration", i.e time to reach the peak plasma concentration of a drug after oral administration (C_{max}) and MRT corresponds to "mean residence time", i.e the average total time molecules of a given dose spend in the body. This can only be measured after instantaneous administration.

Other pharmacokinetics parameters useful according to the invention are represented by:

AUC, which corresponds to "area under the curve", i.e the integral of the concentration-time curve (after a single dose or in steady state). In particular, AUC_{0-t} is the area under the curve up to the last point and $AUC_{0-\infty}$ is the area under the curve up to infinite.

C_{max}, which corresponds to "peak concentration", i.e. the peak plasma concentration of a drug after oral administration.

$t_{1/2}$, which corresponds to "biological half-time", i.e. the time required for the concentration of the drug to reach half of its original value.

Xu_{0-36h} (ng), which corresponds to "urinary excretion", i.e. the active ingredient metabolite urinary excretion during 36 hours time.

T_{lag}, which corresponds to lag time, i.e. the time from administration of a drug to first quantifiable concentration.

CI, which corresponds to "confidence intervals", i.e. a particular kind of interval estimate of a population parameter used to indicate the reliability of an estimate.

CV, which corresponds to "coefficient of variation" provides a relative measure of data dispersion with reference to the mean.

Dissolution Test Method

Tablets according to the present invention undergo to dissolution test to verify the formulation capacity in modulating and controlling the rate by which the active ingredient is leaked by the device or dosage form in the environmental medium, generally a buffered solution simulating gastric or intestinal juices.

The dissolution test is performed by introducing individual tablets in a glace vessel containing from 500 to 1000 ml of a buffered solution set to different pH conditions (pH 1, 6.4 and

7.2 are the pH condition generally used in this test applications), so that the whole digestive tract pH conditions, from stomach to large intestine, should be reproduced. To simulate the human body conditions, the test is carried out at a temperature of 37° C.±2° C. and at predetermined time periods samples of the dissolution medium are withdrawn to detect the percentage of active ingredient dissolved over time.

The tablets according to the present invention, when designed to be used to treat inflammatory bowel disease, in principle have to show a good resistance, thanks to the polymeric film resistant to the low pH conditions (intended as <5 to simulate the gastric environment) applied to cover the tablet surface, resistance which last at least for two hours; to target the large intestinal sectors, also the pH condition of 6.4 shown unsuitability to determine a drug leakage from the administration device for a short exposition time and only mediums at pH 7.2 have been able to determine an active ingredient dissolution at a progressive and quite constant rate during a timeframe from 6 to 12 hours; the dissolution percentage obtained with this tablet formulation were below 15% at first hour sampling, below 25% at second hour sampling, then values were in the range 25% to 55% at fourth hour and a dissolution greater than 80% was achieved at 8^{th} hour sampling.

Bioavailability Study

Bioavailability profile of budesonide extended release compositions (6 mg and 9 mg tablets) vs controlled ileal release formulation (Entocort® 3×3 mg capsules) in healthy volunteers is carried out. The objectives of the study are to compare the bioavailability and PK profile of a 9 mg budesonide extended release tablet formulation of the invention (herein after referred to as T1) versus the market reference formulation, Entocort® EC 3×3 mg capsules (Astra-Zeneca) (herein after referred to as R) and versus a 6 mg budesonide formulation of the invention (herein after referred to as T2).

The primary end-point is comparing bioavailability rate through the PK parameters of plasma budesonide C_{max} and T_{max} after T1 formulation versus reference formulation.

The secondary end-point is comparing bioavailability extent through plasma budesonide AUC_{0-t} after T1 formulation versus reference formulation; comparing bioavailability extent through the PK parameters of plasma budesonide AUC_{0-t} after T1 formulation versus T2 formulation; descriptive pharmacokinetics of budesonide; evaluation of main budesonide metabolite excretion in urine and safety of the test and reference formulations.

Budesonide MMX™ extended release tablets 9 mgs (T1) and 6 mgs (T2) were orally administered in a single dose under fasting conditions in different study periods with a wash-out interval of at least 5 days. One tablet of T1 (batch MV084) or T2 (batch TV158) was administered together with 240 mL of mineral water; the subjects were instructed to swallow the whole tablet without chewing.

The reference therapy was Entocort® EC 3×3 mg capsules (MP0077; Astra-Zeneca, Sweden), orally administered in a single dose under fasting conditions together with 240 mL of mineral water; the subjects were instructed to swallow the whole tablet without chewing.

Results:

After administration under fasting conditions in 3 consecutive study periods of a single dose of budesonide MMX™ extended release tablets 9 mg (T1), 6 mg (T2) of the invention and Entocort EC 3×3 mg capsules (R) the PK of budesonide was found significantly different. Mean±SD (CV %) of plasma budesonide and urine budesonide metabolite PK parameters are summarised in the tables 1-4 below for the PP population (N=12) and PP-control population (N=11).

TABLE 1

Mean ± SD (CV %) budesonide PK parameters after administration of T1, T2 and R

	MMX ™ 9 mg (T1)	MMX ™ 6 mg (T2)	Entocort ®EC 3 × 3 mg (R)
PP-population (N = 12)			
T_{max} (h)	13.3 ± 5.9 (44.5)	11.4 ± 5.1 (44.4)	4.8 ± 1.4 (28.6)
C_{max} (pg/mL)	1348.8 ± 958.8 (71.1)	1158.5 ± 532.4 (46.0)	1555.9 ± 588.0 (37.8)
AUC_{0-t} (pg × h/mL)	13555.9 ± 7816.9 (57.7)	10818.3 ± 4401.6 (40.7)	13394.6 ± 5983.0 (44.7)
$AUC_{0-\infty}$ (pg × h/mL)	16431.2 ± 10519.8 (64.0)	11533.6 ± 4738.5 (41.1)	14057.0 ± 6378.7 (45.4)
C_{max} (pg/mL)/dose	149.9 ± 106.5 (71.1)	193.1 ± 88.7 (46.0)	172.9 ± 65.3 (37.8)
AUC_{0-t} (pg × h/mL)/dose	1506.2 ± 868.5 (57.7)	1803.0 ± 733.6 (40.7)	1488.3 ± 664.8 (44.7)
$t_{1/2}$(h)	8.2 ± 3.7 (44.7)	6.6 ± 2.4 (36.8)	7.7 ± 1.8 (23.1)
MRT (h)	21.4 ± 6.8 (31.5)	17.0 ± 5.7 (33.7)	11.6 ± 2.7 (23.1)
PP-control population (N = 11)			
T_{max} (h)	12.8 ± 6.0 (46.7)	11.0 ± 5.1 (46.4)	4.6 ± 1.4 (29.4)
C_{max} (pg/mL)	1427.3 ± 964.3 (67.6)	1154.9 ± 558.2 (48.3)	1549.0 ± 616.2 (39.8)
AUC_{0-t} (pg × h/mL)	13963.7 ± 8063.4 (57.7)	10331.4 ± 4264.1 (41.3)	13741.1 ± 4147.5 (44.7)
$AUC_{0-\infty}$ (pg × h/mL)	17041.8 ± 10807.8 (63.4)	11533.6 ± 4738.5 (41.1)	14462.8 ± 6572.3 (45.4)
C_{max} (pg/mL)/dose	158.6 ± 107.1 (67.6)	192.5 ± 93.0 (48.3)	172.1 ± 68.5 (39.8)
AUC_{0-t} (pg × h/mL)/dose	1551.5 ± 895.9 (57.7)	1721.9 ± 710.7 (41.3)	1526.8 ± 683.1 (44.7)
$t_{1/2}$(h)	8.4 ± 3.7 (44.0)	6.6 ± 2.4 (36.8)	7.9 ± 1.7 (21.0)
MRT (h)	21.4 ± 7.1 (33.1)	17.0 ± 5.7 (33.7)	11.8 ± 2.7 (23.1)

TABLE 2

Mean ± SD (CV %) 6-β-hydroxy-budesonide cumulative excretion ($Xu_{0-36\ h}$) after administration of T1, T2 and R

	MMX ™ 9 mg (T1)	MMX ™ 6 mg (T2)	Entocort ®EC 3 × 3 mg (R)
PP-population (N = 12)			
$Xu_{0-36\ h}$ (ng)	111061.9 ± 53992.6 (48.6)	76683.4 ± 31879.4 (41.6)	161535.4 ± 60309.8 (37.3)
$Xu_{0-36\ h}$ (ng)/dose	12340.2 ± 5999.2 (48.6)	12780.6 ± 5313.2 (41.6)	17948.4 ± 6701.1 (37.3)
PP-control population (N = 11)			
$Xu_{0-36\ h}$ (ng)	114449.9 ± 55273.9 (48.3)	74729.9 ± 32673.4 (43.7)	164572.0 ± 62283.9 (37.8)
$Xu_{0-36\ h}$ (ng)/dose	12716.6 ± 6141.5 (48.3)	12455.0 ± 5445.6 (43.7)	18285.8 ± 6920.4 (37.8)

TABLE 3

Main individual and mean budesonide PK parameters after administration of MMX ™ 9 mg extended release tablets T1

Subject	T_{max} (h)	C_{max} (pg/mL)	AUC_{0-t} (pg × h/mL)	$AUC_{0-\infty}$ (pg × h/mL)	$t_{1/2}$ (h)	MRT (h)	C_{max}/dose (pg/mL)	AUC_{0-t}/dose (pg × h/mL)
1	12	1127.8	8744.8	9287.9	5.9	16.4	125.3	971.6
2	18	484.7	9070.4	9713.9	5.3	21.2	53.9	1007.8
3	16	960.4	16569.5	20388.6	10.7	24.6	106.7	1841.1
4	16	949.3	14563.4	18683.2	10.9	28.1	105.5	1618.2
5	6	1692.8	11852.4	12202.8	3.9	13.9	188.1	1316.9
6	7	1472.5	8374.0	10125.2	11.5	18.3	163.6	930.4
8	14	1350.7	9282.6	9857.2	5.7	16.6	150.1	1031.4
9	6	894.9	5957.2	6608.2	5.0	13.5	99.4	661.9
10	24	924.5	18026.7	30408.7	15.7	37.5	102.7	2003.0
11	6	4227.2	35119.3	42027.4	11.1	22.3	469.7	3902.2
12	16	941.3	8946.6	9458.5	5.9	20.2	104.6	994.1
107	18	1159.2	16164.1	18412.6	6.4	24.4	128.8	1796.0
PP population, N = 12								
MEAN	13.3	1348.8	13555.9	16431.2	8.2	21.4	149.9	1506.2
SD	5.9	958.8	7816.9	10519.8	3.7	6.8	106.5	868.5
CV %	44.5	71.1	57.7	64.0	44.7	31.5	71.1	57.7
MIN	6	484.7	5957.2	6608.2	3.9	13.5	53.9	661.9
MAX	24	4227.2	35119.3	42027.4	15.7	37.5	469.7	3902.2
N	12	12	12	12	12	12	12	12
PP-control population, N = 11*								
MEAN	12.8	1427.3	13963.7	17041.8	8.4	21.4	158.6	1551.5
SD	6.0	964.3	8063.4	10807.8	3.7	7.1	107.1	895.9
CV %	46.7	67.6	57.7	63.4	44.0	33.1	67.6	57.7
MIN	6	894.9	5957.2	6608.2	3.9	13.5	99.4	661.9
MAX	24	4227.2	35119.3	42027.4	15.7	37.5	469.7	3902.2
N	11	11	11	11	11	11	11	11

*Subject 02 not included in calculations

TABLE 4

Main budesonide PK parameters after administration of MMX ™ 6 mg extended release tablets T2

Subject	T_{max} (h)	C_{max} (pg/mL)	AUC_{0-t} (pg × h/mL)	$AUC_{0-\infty}$ (pg × h/mL)	$t_{1/2}$ (h)	MRT (h)	C_{max}/dose (pg/mL)	AUC_{0-t}/dose (pg × h/mL)
1	14	498.1	4095.2	4617.4	6.9	19.1	83.0	682.5
2	16	1197.4	16173.8	—	—	—	199.6	2695.6
3	7	1146.8	11999.5	13717.5	9.3	20.5	191.1	1999.9
4	10	1330.4	9354.8	10383.5	5.9	13.7	221.7	1559.1
5	9	1938.4	13755.9	14299	6.4	12.5	323.1	2292.7
6	6	1300.4	8986.8	9398.9	3.9	11.7	216.7	1497.8
8	10	1781.2	14493.0	15234.8	6.9	13.1	296.9	2415.5
9	7	400.8	3314.1	3643.1	3.3	12.4	66.8	552.4
10	14	869.6	12647.3	15596.5	11.7	25.0	144.9	2107.9
11	8	1948.6	16309.7	17261.7	5.8	14.5	324.8	2718.3
12	12	672.6	6511.4	7292.6	4.7	15.3	112.1	1085.2
107	24	817.2	12178.1	15424.7	7.9	28.9	136.2	2029.7
PP population, N = 12								
MEAN	11.4	1158.5	10818.3	11533.6	6.6	17.0	193.1	1803.0
SD	5.1	532.4	4401.6	4738.5	2.4	5.7	88.7	733.6
CV %	44.4	46.0	40.7	41.1	36.8	33.7	46.0	40.7
MIN	6	400.8	3314.1	3643.1	3.3	11.7	66.8	552.4
MAX	24	1948.6	16309.7	17261.7	11.7	28.9	324.8	2718.3
N	12	12	12	11	11	11	12	12
PP-control population, N = 11*								
MEAN	11	1154.9	10331.4	11533.6	6.6	17.0	192.5	1721.9
SD	5.1	558.2	4264.1	4738.5	2.4	5.7	93.0	710.7
CV %	46.4	48.3	41.3	41.1	36.8	33.7	48.3	41.3
MIN	6	400.8	3314.1	3643.1	3.3	11.7	66.8	552.4
MAX	24	1948.6	16309.7	17261.7	11.7	28.9	324.8	2718.3
N	11	11	11	11	11	11	11	11

*Subject 02 not included in calculations

Pharmacokinetic Results:

After administration under fasting conditions in 3 consecutive study periods of a single dose of Budesonide MMX™ extended release tablets 9 mg (T1), 6 mg (T2) and Entocort® EC 3×3 mg capsules (R) the PK of budesonide was found significantly different. Mean±SD (CV %) of plasma budesonide and urine budesonide-metabolite PK parameters are summarised in the table below for the PP population (N=12).

Results obtained in the present study on the PP population (see table above) were confirmed by the results of the PK analysis on the PP-control population (i.e. after excluding subject randomisation Nr. 02, who showed pre-dose detectable levels) and therefore were regarded as the primary results of the study, as per protocol. Inter-subject variability was higher for the MMX™ tablet formulation than for Entocort® EC, a finding that can be explained by the broader intestinal tract involved in the drug release from the test products (whole colon and sigmoid) as compared to the reference (terminal ileum, ascending colon) and from the absence of dose fractionation in the MMX™ formulations.

Although budesonide elimination is constant and no differences among formulations were found for $t_{1/2}$ values, the different release/absorption behaviour of MMX™ tablets and Entocort® EC capsules was apparent from MRT values which were higher for the MMX™ formulations.

Analysis on T1 and R C_{max} and T_{max}, showed a different rate of absorption for MMX™ tablets 9 mg (T1) with respect to Entocort® EC 3×3 mg capsules (R). T1 had a lower budesonide concentration peak than R as confirmed by a PE % of 79% and 90% CI limits of 63-100%, and a significantly higher T_{max} (13.3 h for T1 vs. 4.8 h for R). Extent of absorption calculated from the AUC_{0-t} of budesonide after administration of T1 and R was also significantly different. T1 bioavailability over the 36 h period was lower than R bioavailability (PE=91%; 90% CI limits: 77-108%). Therefore, T1 and R were found to be non-bioequivalent.

Analysis on Tmax, and dose-normalized C_{max}/dose and AUC_{0-t}/dose showed differences in rate and extent of absorption also for T1 vs. T2, As expected, T1 had a higher concentration peak and bioavailability than T2, although a linear relationship with dose was not observed (PE for C_{max}/dose=75%; 90% CI limits: 59-95%, PE for AUC_{0-t}/dose=80%; 90% CI limits: 67-94%). Therefore, T1 and T2 were found non-bioequivalent.

Tmax differences between T1 and T2 were not statistically significant (p value from t test=0.2244). Analysis on budesonide metabolite urinary excretion (Xu_{0-36h}), showed a different excretion among formulations, with a bioequivalence not satisfied for T1 vs. R (PE=66%; 90% CI limits: 54-81%) and almost achieved for T1 vs. T2 (PE=96%, 90% CI limits: 79-117%).

Safety Results:

The safety profile of the 3 formulations was similar. Only 3 AEs occurred during the study, 1 with T2 formulation and 2 with R formulation. Of these 3 AEs, only 1 with R formulation (i.e. headache) was judged possibly related to treatment. No meaningful effect of treatment on vital signs, ECGs or laboratory parameters was observed.

Conclusions:

The formulation Budesonide MMX™ extended release tablets 9 mg was found not bioequivalent to the reference Entocort® EC 3×3 mg capsules in terms of rate and extent of bioavailability since the 90% CI for C_{max} and AUC_{0-t} did not fall within the 80-125% limits required by current guidelines, and T_{max}, was statistically different between MMX™ 9 mg and Entocort® EC 3×3 mg. This finding is explained by the different release behaviour of the test and reference formulations which determines different profiles of budesonide absorption. When MMX™ 9 mg and 6 mg tablet formulations were compared to evaluate dose proportionality, whereas no significant difference was found for T_{max}, the analysis of dose normalised C_{max}, AUC_{0-t} indicated lack of equivalence since the 90% CI for these parameters did not fall within the 80-125% limits required by current guidelines. but overlapped them.

The safety profile of the 3 formulations was similar and very good.

Pharmaco-scintigraphic and Kinetic Study

A single dose, pharmaco-scintigraphic and kinetic study of the gastrointestinal transit and release of a ^{152}Sm-labelled controlled release formulation of budesonide in 12 fasting male healthy volunteers is carried out.

The objective of the study is to demonstrate and quantify, by pharmaco-scintigraphy and PK analysis, the release and absorption of budesonide in the target region.

Each subject received 1 tablet of budesonide MMX™ 9 mg and an average radioactivity dose of 1.118+0.428 MBq as $^{153}Sm_2O_3$ To define the GI transit behaviour of the study formulation, images were recorded at approximately 20 min intervals up to 3 h post-dose and 30 min intervals up to 10 h. Further acquisitions were taken at 12 and 24 h post-dose. The following Regions of Interest (ROIs) were defined: stomach, small intestine, terminal ileum, ileo-caecal junction and caecum, ascending, transverse, descending and sigmoid colon. Quantification of the distribution were achieved by measuring the count rates recorded from the ROIs.

Budesonide plasma levels were detected between the 1st and the 12th h post-administration. On the average the appearance of drug plasma levels occurred in 6.79±3.24 h (T_{lag}). Peak time (T_{max}) averaged 14.00±7.73 h, with mean concentration (C_{max}) of 1768.7±1499.8 pg/mL. Measured average plasma AUC_t in 24 h was 15607±14549 pgxh/mL. The difference $T_{max}-T_{lag}$ accounted for 7.21±5.49 h, a time period which may be representative of the release time of the active from the tablet.

The following table 5 summarises the main kinetic evidence:

TABLE 5

N = 12	C_{max} (pg/mL)	T_{max} (h)	AUC_t (pg × h/mL)	T_{lag} (h)	$T_{max}-T_{lag}$ (h)
Mean	1768.7	14.00	15607	6.79	7.21
SD	1499.8	7.734	14549	3.24	5.49
CV	84.80	55.24	93.22	47.66	76.13
Min	337.3	5	2465	1	0
Max	4756.3	24	53163	12	17

Combining the scintigraphic with the kinetic evidence, drug absorption during the time interval of the radioactivity location in the target ROI (i.e. the region comprised between the ascending and the descending-sigmoid colon) could be approximately calculated to amount to 95.88±4.19% of the systemically bioavailable dose.

Results:

The systemic availability of budesonide MMX™ 9 mg is mostly ascribable to the drug absorption throughout the whole colon including the sigmoid, see table 6 below:

TABLE 6

	AUC_{colon}	AUC_t	$AUC_{colon}/AUC_t \times 100$
Mean	15113.46	15606.52	95.88
SD	14401.79	14549.23	4.19
Min	2464.80	2464.80	84.93
Max	52376.20	53162.50	100.00

EXAMPLE 1

2.7 kg of budesonide, 3.0 kg of lecithin (amphiphilic matrix forming material) and 3.0 kg of stearic acid (lipophilic matrix forming material) are mixing after sieving till an homogeneous mixture is obtained; then add 39.0 kg of inert, functional excipients and 9.0 kg of low viscosity hydroxypropylcellulose (binder) and mix for 10 minutes before adding purified water and kneading to a suitable consistence. Then pass the granulate through a rotating granulator equipped with the suitable screen and transfer the granulate to the fluid bed drier to lower the residual moisture content under 3%. After a new sieving on the dry, the granulate is added of 9.0 kg of hydroxypropylcellulose (hydrophilic matrix forming material) and the suitable amount of functional excipients (in particular, microcrystalline cellulose, lactose and silicon dioxide) and, after 15 minutes of mixing, magnesium stearate in a suitable quantity to act as lubricant is added.

After a final blending, tablets of around 300 mg of unitary weight are generated.

The core are then subjected to be coated with a suspension obtained introducing into a stainless steel container 5.8 kg of Eudragit™ (methacrylate copolymers), 0.6 kg of triethylcitrate and 3.0 kg of dyes and talc, using alcohol as solvent.

The mean dissolution percentage (as average of six or more tablets) obtained with this tablet formulation were around 10-20% at second hour sampling, in the range 25% to 65% at fourth hour and a dissolution greater than 80% was achieved at 8^{th} hour sampling.

EXAMPLE 2

Component	mg/tablet
Tablet	
Budesonide	9.0
Stearic Acid (lipophilic matrix forming materials)	10.0
Lecithin (amphiphilic matrix forming material)	10.0
Microcristalline cellulose	156.0
Hydroxypropylcellulose	60.0
Lactose monohydrate	50.0
Silicon dioxide	2.0
Magnesium stearate	3.0
Coating materials	
Eudragit L100 (acrylic and methacrylic copolymer)	14.0
Eudragit S100 (acrylic and methacrylic copolymer)	12.0
Talc	7.9
Titanium dioxiede	4.5
Triethylcitrate	1.6
Alcohol	q.s.

The coating of industrial scale tablets of batch MV084 contained 8.0 mg of Eudragit L100 and 8.0 mg of Eudragit 5100 (instead of 14.0 mg and 12.0 mg, respectively) with an individual weight of about 330 mg.

According to the present invention, coated tablets individually weighing about 340 mg are obtained.

The above described dissolution test is performed on the tablets of Example 2. The results are the following (indicated as average value):

after 2 hours at pH 1	resistent (<5%)
after 1 hour at pH 6.4	resistent (<5%)
after 2 hours at pH 7.2	15%
after 4 hours at pH 7.2	37%
after 8 hours at pH 7.2	91%

EXAMPLE 3

Budesonide (3.0 kg) is mixed with soybean Lecithin (5.0 kg) till an homogeneous mixture is obtained. Then carnauba wax (2.0 kg) and stearic acid (2.0 kg) sieved through a fine screen are added. After mixing, the powders are added with other functional excipients and kneaded with a binder solution obtained by dissolving medium viscosity polyvinylpirrolidone in water. After drying in a fluid bed and milling throughout a suitable screen, hydroxypropylmethylcellulose (35.0 kg) and other excipients, including magnesium stearate as lubricant, in a suitable quantity are added and the mixture is blended till an homogeneous powder dispersion is obtained.

The powder mixture is subjected to compression in a rotating tabletting machine and the tablets so obtained are coated in a pan coat with a gastroresistant composition containing Eudragit™, plasticizers, dyes and pigments.

According to the present example, coated tablets individually weighing around 105 mg are obtained.

The results of the above described dissolution test are the following (indicated as average value of at least six tablets):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	9%
after 4 hours at pH 7.2	28%
after 8 hours at pH 7.2	86%

EXAMPLE 4

50 g of diethylene glycol monoethyl ether are homogeneously distributed on 500 g of microcrystalline cellulose; then 100 g of Budesonide are added, mixing to complete homogenization. This mix is further added with 400 g of Budesonide, then dispersed in a blender containing 100 g of carnauba wax and 100 g of stearic acid preheated at a temperature of 60° C. After kneading for 5 minutes, the mixture is cooled to room temperature and extruded in granules of size below 1 mm. A suitable mixer is loaded with the matrix granules prepared as above and the following amounts of hydrophilic excipients: 1500 g of hydroxypropyl methylcellulose and 500 g of Policarbophil™ are added. The components are mixed until homogeneous dispersion of the matrices, then added with 2450 g of microcrystalline cellulose, 400 g of lactose, 100 g of colloidal silica and 50 g of magnesium stearate. After further 5 minute mixing, the mix is tableted to unitary weight of 250 mg/tablet.

Tablets are then subjected to coating using a suspension n containing polyacrylate and poly methacrilate copolymers in addition to other dyes, plasticizers and colouring agents in solvent (ethylic alcohol).

The results of the dissolution test performed on these coated tablets are the following (indicated as average value of at least six tablets):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	11%
after 4 hours at pH 7.2	32%
after 8 hours at pH 7.2	76%

What is claimed is:

1. An oral pharmaceutical composition administered to a human, wherein said oral pharmaceutical composition is in the form of a tablet, said tablet comprising:

(a) a tablet core comprising:

(i) 9 mg of budesonide; and

(ii) a macroscopically homogenous composition comprising stearic acid and/or salt thereof, lecithin, and hydroxypropyl cellulose, wherein said budesonide is dispersed in said macroscopically homogeneous composition; and

(b) a coating on said tablet core consisting essentially of a gastro-resistant film, wherein said gastro-resistant film consists essentially of a mixture of 8 mg of a first methacrylic acid copolymer and 8 mg of a second methacrylic acid copolymer, and

wherein said oral pharmaceutical composition provides a T_{lag} of said budesonide in said human of about 6.79±3.24 hours following said administration of said oral pharmaceutical composition to said human.

2. An oral pharmaceutical composition administered to a human according to claim **1**, wherein said oral pharmaceutical composition administered to said human further provides a C_{max} of said budesonide of about 1768.7±1499.8 pg/mL in said human following administration of said oral pharmaceutical composition to said human.

3. An oral pharmaceutical composition administered to a human, wherein said oral pharmaceutical composition is in the form of a tablet, said tablet comprising:

(a) a tablet core comprising:

(i) 9 mg of budesonide; and

(ii) a macroscopically homogenous composition comprising stearic acid and/or salt thereof, lecithin, and hydroxypropyl cellulose, wherein said budesonide is dispersed in said macroscopically homogeneous composition; and

(b) a coating on said tablet core consisting essentially of a gastro-resistant film, wherein said gastro-resistant film consists essentially of a mixture of 8 mg of a first methacrylic acid copolymer and 8 mg of a second methacrylic acid copolymer, and

wherein said oral pharmaceutical composition provides a (T_{max}-T_{lag}) of said budesonide in said human of about 7.21±5.49 hours following said administration of said oral pharmaceutical composition to said human.

4. An oral pharmaceutical composition administered to a human according to claim **3**, wherein said oral pharmaceutical composition administered to said human further provides a C_{max} of said budesonide of about 1768.7±1499.8 pg/mL in said human following administration of said oral pharmaceutical composition to said human.

5. An oral pharmaceutical composition administered to a human, wherein said oral pharmaceutical composition is in the form of a tablet, said tablet consisting essentially of:

(a) a tablet core comprising:

(i) 9 mg of budesonide; and

(ii) a macroscopically homogenous composition comprising stearic acid and/or salt thereof, lecithin, and hydroxypropyl cellulose, wherein said budesonide is dispersed in said macroscopically homogeneous composition; and

(b) a coating on said tablet core consisting essentially of a gastro-resistant film, wherein said gastro-resistant film consists essentially of a mixture of 8 mg of a first methacrylic acid copolymer and 8 mg of a second methacrylic acid copolymer, and

wherein said oral pharmaceutical composition provides a T_{lag} of said budesonide in said human of about 6.79±3.24 hours following said administration of said oral pharmaceutical composition to said human.

6. An oral pharmaceutical composition administered to a human according to claim **5**, wherein said oral pharmaceutical composition administered to said human further provides a C_{max} of said budesonide of about 1768.7±1499.8 pg/mL in said human following administration of said oral pharmaceutical composition to said human.

7. An oral pharmaceutical composition administered to a human, wherein said oral pharmaceutical composition is in the form of a tablet, said tablet consisting essentially of:

(a) a tablet core comprising:

(i) 9 mg of budesonide; and

(ii) a macroscopically homogenous composition comprising stearic acid and/or salt thereof, lecithin, and hydroxypropyl cellulose, wherein said budesonide is dispersed in said macroscopically homogeneous composition; and

(b) a coating on said tablet core consisting essentially of a gastro-resistant film, wherein said gastro-resistant film consists essentially of a mixture of 8 mg of a first methacrylic acid copolymer and 8 mg of a second methacrylic acid copolymer, and

wherein said oral pharmaceutical composition provides a (T_{max}-T_{lag}) of said budesonide in said human of about 7.21±5.49 hours following said administration of said oral pharmaceutical composition to said human.

8. An oral pharmaceutical composition administered to a human according to claim **7**, wherein said oral pharmaceutical composition administered to said human further provides a C_{max} of said budesonide of about 1768.7±1499.8 pg/mL in said human following administration of said oral pharmaceutical composition to said human.

9. An oral pharmaceutical composition administered to a human, wherein said oral pharmaceutical composition is in the form of a tablet, said tablet comprising:

(a) a tablet core comprising:

(i) 9 mg of budesonide; and

(ii) a macroscopically homogenous composition comprising stearic acid and/or salt thereof, lecithin, and hydroxypropyl cellulose, wherein said budesonide is dispersed in said macroscopically homogeneous composition; and

(b) a coating on said tablet core consisting essentially of a gastro-resistant film, wherein said gastro-resistant film consists essentially of a mixture of 8 mg of a first methacrylic acid copolymer and 8 mg of a second methacrylic acid copolymer, and

wherein said oral pharmaceutical composition provides a T_{lag} of said budesonide in said human of from about 1 hour to about 12 hours following said administration of said oral pharmaceutical composition to said human.

10. An oral pharmaceutical composition administered to a human according to claim **9**, wherein said oral pharmaceutical composition administered to said human further provides a C_{max} of said budesonide of about 1768.7±1499.8 pg/mL in

said human following administration of said oral pharmaceutical composition to said human.

11. An oral pharmaceutical composition administered to a human, wherein said oral pharmaceutical composition is in the form of a tablet, said tablet consisting essentially of:

(a) a tablet core comprising:

(i) 9 mg of budesonide; and

(ii) a macroscopically homogenous composition comprising stearic acid and/or salt thereof, lecithin, and hydroxypropyl cellulose, wherein said budesonide is dispersed in said macroscopically homogeneous composition; and

(b) a coating on said tablet core consisting essentially of a gastro-resistant film, wherein said gastro-resistant film consists essentially of a mixture of 8 mg of a first methacrylic acid copolymer and 8 mg of a second methacrylic acid copolymer, and

wherein said oral pharmaceutical composition provides a T_{lag} of said budesonide in said human of from about 1 hour to about 12 hours following said administration of said oral pharmaceutical composition to said human.

12. An oral pharmaceutical composition administered to a human according to claim **11**, wherein said oral pharmaceutical composition administered to said human further provides a C_{max} of said budesonide of about 1768.7±1499.8 pg/mL in said human following administration of said oral pharmaceutical composition to said human.

* * * * *

EXHIBIT F

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Villa et al.
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(45) **Date of Reissued Patent: *Nov. 13, 2012**

(54) **CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION**

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(*) Notice: This patent is subject to a terminal disclaimer.

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(57) **ABSTRACT**

Controlled release and taste masking compositions containing one or more active principles inglobated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally inglobated or dispersed in hydrophilic matrices. The use of a plurality of systems for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract.

11 Claims, No Drawings

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CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITION

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This application is a continuation-in-part application of U.S. application Ser. No. 10/009,532, filed Dec. 12, 2001, which is a national stage of International Application No. PCT/EP00/05356 on Jun. 9, 2000, now U.S. Pat. No. 7,431, 943, the entire content of which International Application is hereby incorporated by reference and priority to which is hereby claimed.

The present invention relates to controlled release and taste masking compositions containing budesonide as active ingredient incorporated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally incorporated or dispersed in hydrophilic matrices. The use of a plurality of systems mechanism for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract, and it also allows the oral administration of active principles having unfavourable taste characteristics or irritating action on the mucosae of the administration site, particularly in the buccal or gastric area.

The compositions of the invention are suitable to the oral administration or the efficaciously deliver the active ingredient acting topically at some areas of the gastrointestinal tract.

TECHNOLOGICAL BACKGROUND

The preparation of a sustained, controlled, delayed, extended or anyhow modified release form can be carried out according to different techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of bioerodible matrices, which are capable of being degraded by the anzimes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Inert matrices, for example, generally entail non-linear, but exponential, release of the active ingredient.

Hydrophilic matrices: have a linear behaviour until a certain fraction of active ingredient has been released, then significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "sire-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated

The same notion of canalization of an inert matrix is described in U.S. Pat. No. 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials. EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form. The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533, (1998) which improves the application through an annealing technique of the inert polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises: —dissolution of the active ingredient with gastro resistant hydrophilic polymers in organic solvents; —dying of said suspension; —subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application. EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid. WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of the active ingredient. When preparing sustained-, controlled-release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release. Said object has been attained according to the present invention, through the combination of an amphiphilic matrix inside an inert matrix, the latter formulated with a lipophilic polymer in a superficial hydrophilic matrix. The compositions of the invention are characterized by the absence of a first phase in which the medicament superficially present on the matrix is quickly solubilized, and by the fact the amphiphilic layer compensate the lack of affinity of the aqueous solvent with the lipophilic compounds forming the inner inert matrix.

DISCLOSURE OF THE INVENTION

The invention provides controlled release and taste masking oral pharmaceutical compositions containing as active ingredient budesonide comprising:

a) a matrix consisting of lipophilic compounds with melting point lower than 90[deg.] C. and optionally by amphiphilic compounds in which the active ingredient is at least partially incorporated;

b) an amphiphilic matrix;

c) an outer hydrophilic matrix in which the lipophilic matrix and the amphiphilic matrix are dispersed;

d) optionally other excipients.

A particular aspect of the invention consists of controlled release oral compositions containing as active ingredient budesonide comprising:

a) a matrix consisting of amphiphilic compounds and lipophilic compounds with melting point below 90° C. in which the active ingredient is at least partially incorporated;

b) an outer hydrophilic matrix in which the lipophilic/amphiphilic matrix is dispersed, preferably by mixing;

c) optionally other excipients.

A further aspect of the invention provides taste masking oral pharmaceutical compositions budesonide containing comprising:

an inert or lipophilic matrix consisting of C6-C20 alcohols or C8-C20 fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six:

an amphiphilic matrix consisting of polar lipids of type I or II or glycols partially etherified with C1-C4 alkyl chains;

an outer hydrophilic matrix containing the above matrices, mainly formed by saccharide, dextrin, polyalcohol or cellulose compounds or by hydrogels or their mixtures;

optional excipients to give stability to the pharmaceutical formulation.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be prepared by a method comprising the following steps:

a) the active ingredient, represented by budesonide, is first inglobated by simple kneading or mixing in a matrix or coating consisting of compounds having amphiphilic properties, which will be further specified below. The active ingredient can be mixed with the amphiphilic compounds without the aid of solvents or with small amounts of water-alcoholic solvents.

b) the matrix obtained as specified under a) is incorporated in a low melting lipophilic excipient or mixture of excipients, if necessary while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion forming an inert matrix which can be reduced in size to obtain inert matrix granules containing the active ingredient particles.

c) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients. The mixture is then subjected to compression or tabletting. This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix. The amphiphilic compounds which can be used according to the invention comprise polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolainine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol®) The lipophilic matrix consists of substances selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerides, the polyethoxylated derivatives thereof, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40 to 90° C., preferably from 60 to 70 C. If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside. An amphiphilic matrix with high content in active ingredient, typically from 5 to 95% w/w, in particular from 20 to 70%, is first prepared by dispersing the active ingredient in a mixture of amphiphilic compounds, such as lecithin, other type II polar lipids, surfactants, or in diethylene glycol monoethyl ether; the resulting amphiphilic matrix is then mixed or kneaded, usually while hot, with lipophilic compounds suitable to form an inert matrix, such as saturated or unsaturated fatty acids, such as palmitic, stearic, myristic, lauric, laurylic, or oleic acids or mixtures thereof with other fatty acids with shorter chain, or salts or alcohols or derivatives of the cited fatty acids, such as mono-, di-, or triglycerides or esters with polyethylene glycols, alone or in combination with waxes, ceramides, cholesterol derivatives or other apolar lipids in various ratios so that the melting or softening points of the lipophilic compounds mixtures is within the range of 40 to 90 C, preferably from 60 to 70 C. Alternatively, the order of formation of the inert and amphiphilic matrices can be reversed, incorporating the inert matrix inside the amphiphilic compounds. The resulting inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture. The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which when passing from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves. Examples of hydrogels which can be used according to the invention are compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid. In case of taste-masking formulations, the use of polyalcohols such as xylitol, maltitol and mannitol as hydrophilic compounds can also be advantageous. The lipophilic matrix granules containing the active ingredient are mixed with the hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:50 (lipophilic matrix: hydrophilic matrix). Part of the active ingredient can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitablets. The compression of the mixture of lipophilic and/or amphiphilic matrix, hydrogel-forming compound and, optionally, active ingredient not inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix. A similar result can also be obtained by coating the lipophilic matrix granules with a hydrophilic polymer coating. The tablets obtainable according to the invention are subjected to known coating processes with a gastro-resistant film, consisting of, for example, acrylic and methacrylic acids polymers (Eudragit®) or copolymer or cellulose derivatives, such as cellulose acetophthalate. The composition of the invention can further contain conventional excipients, for example bioadhesive excipients such as chitosans, polyacrylamides, natural or synthetic gums, acrylic acid polymers.

The compositions of the invention are preferably in the form of tablets, capsules or minitablets. In terms of dissolu-

tion characteristics, contact with water or aqueous fluids causes the immediate penetration of water inside the more superficial layer of the matrix which, thanks to the presence of the aqueous solvent, swells due to the distension of the polymeric chains of the hydrogels, giving rise to a high viscosity hydrated front which prevents the further penetration of the solvent itself linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness, until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of inert matrix granules, however induces the diffusion mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient. The presence of the amphiphilic matrix inside the lipophilic matrix inert allows to prevent any unevenness of the release profile of the active ingredient. The surfactants present in the amphiphilic portion promote wettability of the porous canaliculuses which cross the inert matrix preventing or reducing resistance to penetration of the solvent inside the inert matrix. To obtain taste masking tablets, the components of the hydrophilic matrix are carefully selected to minimize the active substance release time through penetration accelerated by the canalization induced by the hydrophilic compound.

EXPERIMENTAL PART

To test the effective ability of the formulations of the invention to modify the release rate and extent of the active ingredient from the dosage form suitable for the drug administration, before any pharmacokinetic study on patients or volunteers, the dissolution test is taken as monitoring and discriminating tool. Dissolution Test Method.

Tablets according to the present invention undergo to dissolution test to verify the formulation capacity in modulating and controlling the rate by which the active ingredient is leaked by the device or dosage form in the environmental medium, generally a buffered solution simulating gastric or intestinal juices.

The dissolution test is performed by introducing individual tablets in a glace vessel containing from 500 to 1000 ml of a buffered solution set to different pH conditions (pH 1, 6.4 and 7.2 are the pH condition generally used in this test applications), so that the whole digestive tract pH conditions, from stomach to large intestine, should be reproduced. To simulate the human body conditions, the test is carried out at a temperature of 37° C.+−<=2° C. and at predetermined time periods samples of the dissolution medium are withdrawn to detect the percentage of active ingredient dissolved over time.

The tablets according to the present invention, when designed to be used to treat inflammatory bowel disease, in principle have to show a good resistance, thanks to the polymeric film resistant to the low pH conditions (intended as <5 to simulate the gastric environment) applied to cover the tablet surface, resistance which last at least for two hours; to target the large intestinal sectors, also the pH condition of 6.4 shown unsuitability to determine a drug leakage from the administration device for a short exposition time and only mediums at pH 7.2 have been able to determine an active ingredient dissolution at a progressive and quite constant rate during a timeframe from 6 to 12 hours; the dissolution percentage obtained with this tablet formulation were below 15% at first hour sampling, below 25% at second hour sampling, then values were in the range 25% to 55% at fourth hour and a dissolution greater than 80% was achieved at 8 hour sampling.

Example 1

2.7 kg of budesonide, 3.0 kg of lecithin (amphiphilic matrix forming material) and 3.0 kg of stearic acid (lipophilic matrix forming material) are mixing after sieving till an homogeneous mixture is obtained; then add 39.0 kg of inert, functional excipients and 9.0 kg of low viscosity hydroxypropylcellulose (binder) and mix for 10 minutes before adding purified water and kneading to a suitable consistence. Then pass the granulate through a rotating granulator equipped with the suitable screen and transfer the granulate to the fluid bed drier to lower the residual moisture content under 3%.

After a new sieving on the dry, the granulate is added of 9.0 kg of hydroxypropylcellulose (hydrophilic matrix forming material) and the suitable amount of functional excipients (in particular, microcrystalline cellulose, lactose and silicon dioxide) and, after 15 minutes of mixing, magnesium stearate in a suitable quantity to act as lubricant is added.

After a final blending, tablets of around 300 mg of unitary weight are generated.

The core are then subjected to be coated with a suspension obtained introducing into a stainless steel container 5.8 kg of Eudragit™ (methacrylate copolymers), 0.6 kg of triethylcitrate and 3.0 kg of dyes and talc, using alcohol as solvent.

The mean dissolution percentage (as average of six or more tablets) obtained with this tablet formulation were around 10-20% at second hour sampling, in the range 25% to 65% at fourth hour and a dissolution greater than 80% was achieved at 8 hour sampling.

Example 2

Component	mg/tablet
Tablet	
Budesonide	9.0
Stearic Acid	10.0
Lecithin	10.0
Microcristalline cellulose	156.0
Hydroxypropylcellulose	60.0
Lactose monohydrate	50.0
Silicon dioxide	2.0
Magnesium stearate	3.0
Coating materials	
Eudragit L100	14.0
Eudragit S100	12.0
Talc	7.9
Titanium dioxiede	4.5
Triethylcitrate	1.6
Alcohol	q.s.

According to the present invention, coated tablets individually weighing about 220 mg are obtained.

The above described dissolution test is performed on the tablets of Example 2.

The results are the following (indicated as average value):

after 2 hours at pH 1	resistant (<5%)
after 1 hour at pH 6.4	resistant (<5%)
after 2 hours at pH 7.2	15%
after 4 hours at pH 7.2	37%
after 8 hours at pH 7.2	91%

Example 3

Budesonide (3.0 kg) is mixed with soybean Lecithin (5.0 kg) till an homogeneous mixture is obtained. Then carnauba wax (2.0 kg) and stearic acid (2.0 kg) sieved through a fine screen are added. After mixing, the powders are added with other functional excipients and kneaded with a binder solution obtained by dissolving medium viscosity polyvinylpyrrolidone in water. After drying in a fluid bed and milling throughout a suitable screen, hydroxypropylmethylcellulose (35.0 kg) and other excipients, including magnesium stearate as lubricant, in a suitable quantity are added and the mixture is blended till an homogeneous powder dispersion is obtained.

The powder mixture is subjected to compression in a rotating tabletting machine and the tablets so obtained are coated in a pan coat with a gastroresistant composition containing Eudragit™, plasticizers, dyes and pigments.

According to the present example, coated tablets individually weighing around 105 mg are obtained.

The results of the above described dissolution test are the following (indicated as average value of at least six tablets):

after 2 hours at pH 1	(<5%) resistant
after 1 hour at pH 6.4	(<5%) resistant
after 2 hours at pH 7.2	9%
after 4 hours at pH 7.2	28%
after 8 hours at pH 7.2	86%

Example 4

50 g of diethylene glycol monoethyl ether are homogeneously distributed on 500 g of microcrystalline cellulose; then 100 g of Budesonide are added, mixing to complete homogenization. This mix is further added with 400 g of Budesonide, then dispersed in a blender containing 100 g of carnauba wax and 100 g of stearic acid preheated at a temperature of 60[deg.] C. After kneading for 5 minutes, the mixture is cooled to room temperature and extruded in granules of size below 1 mm. A suitable mixer is loaded with the matrix granules prepared as above and the following amounts of hydrophilic excipients: 1500 g of hydroxypropyl methylcellulose and 500 g of Policarbophil™ are added. The components are mixed until homogeneous dispersion of the matrices, then added with 2450 g of microcrystalline cellulose, 400 g of lactose, 100 g of colloidal silica and 50 g of magnesium stearate. After further 5 minute mixing, the mix is tableted to unitary weight of 250 mg/tablet.

Tablets are then subjected to coating using a suspension n containing polyacrylate and poly methacrylate copolymers in addition to other dyes, plasticizers and colouring agents in solvent (ethylic alcohol).

The results of the dissolution test performed on these coated tablets are the following (indicated as average value of at least six tablets):

after 2 hours at pH 1	(<5%) resistant
after 1 hour at pH 6.4	(<5%) resistant
after 2 hours at pH 7.2	11%
after 4 hours at pH 7.2	32%
after 8 hours at pH 7.2	76%

EXAMPLE A

500 g of 5-aminosalicylic-acid and 20 of octylonium bromide are mixed with 10 g of soy lecithin dissolved in 50 g of a water:ethyl alcohol 1:3 mixture at about 50° C. After homogenization and drying, the granules of the resulting matrix are treated in a kneader with 20 g of carnauba wax and 50 g of stearic acid, heating until homogeneous dispersion, then cold-extruded into small granules. The inert matrix granules are loaded into a mixer in which 30 g of carbopol 971 P and 65 g of hydroxypropyl methylcellulose "are sequentially added." After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 760 mg/tablet. The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 30%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

EXAMPLE B

50 g of diethylene glycol monoethyl ether are homogeneously distributed on 500 g of microcrystalline cellulose; then 100 g of Budesonide are added, mixing to complete homogenization. This mix is further added with 400 g of Budesonide, then dispersed in a blender containing 100 g of carnauba wax and 100 g of stearic acid preheated at a temperature of 60° C. After kneading for 5 minutes, the mixture is cooled to room temperature and extruded in granules of size below 1 mm.

A suitable mixer is loaded with the matrix granules prepared as above and the following amounts of hydrophilic excipients: 1500 g of hydroxypropyl methylcellulose and 500 g of policarbophil.

The components are mixed until homogeneous dispersion of the matrices, then added with 2450 g of microcrystalline cellulose, 400 g of lactose, 100 g of colloidal silica and 50 g of magnesium stearate. After further 5 minute mixing, the mix is tabletted to unitary weight of 250 mg/tablet.

EXAMPLE C

850 g of metformin are dispersed in a granulator/kneader with 35 g of diethylene glycol monoethyl ether previously melted with 100 g of stearic acid and 55 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 1040 g of formulation are added with 110 g of hydroxypropyl methylcellulose and 20 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 1170 mg/tablet equivalent to 850 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 35%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

EXAMPLE D

120 g of octylonium bromide are dispersed in a granulator/kneader with 30 g of stearic acid and 15 g of beeswax in which 10 g of diethylene glycol monoethylene had previously been melted.

The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 10 g of formulation are added with 5 g of hydroxypropyl methylcellulose and 5 g of policarbophyl, 2 g of magnesium stearate and 3 g of microcrystalline cellulose.

The final mixture is tabletted to unitary weight of 200 mg/tablet equivalent to 120 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 25%; after 180 minutes no more than 50%; after 5 hours no more than 70%.

EXAMPLE E

12 g of diethylene glycol monoethyl ether are loaded on 6 g of microcrystalline cellulose and 6 grams of calcium carbonate, then 100 g of Gabapentin are added and the mixture is homogenized. After that, 800 g of Gabapentin are added which are dispersed in a granulator/kneader with 4.5 g of white wax and 5 g of stearic acid. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 916.5 g of formulation are added with 39.5 g of hydroxypropyl methylcellulose, 10 g of alginic acid, 11 g of magnesium stearate and 6 g of syloid. The final mixture is tabletted to unitary weight of 1000 mg/tablet equivalent to 900 mg of active ingredient.

EXAMPLE F

50 g (25 g) of carbidopa and 200 g (100 g) of levodopa are dispersed in a granulator/kneader with 60 g (30 g) of stearic acid and 30 g (15 g) of yellow wax, in which 10 (5) g of diethylene glycol monoethyl ether had previously been melted.

The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 340 g (170 g) of formulation are added with 20 g (10 g) of hydroxypropyl methylcellulose, 10 g (5 g) of xantangum, 16 g (8 g) of microcrystalline cellulose, 4 g (2 g) of magnesium stearate.

The final mixture is tabletted to unitary weight of 400 (200) mg/tablet equivalent to 50 (25) mg of carbidopa and 200 (–100) mg di levodopa.

EXAMPLE G

4 g of Nimesulide are solubilised in 50 g of diethylene glycol monoethyl ether, then 100 g of microcrystalline cellulose are added to obtain a homogeneous mixture.

The resulting mixture is added in a granulator/kneader with 196 g of Nimesulide, 50 g of stearic acid and 25 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert and amphiphilic matrix system.

425 g of the resulting granulate are added with 60 g of hydroxypropyl methylcellulose, 5 g of policarbophil and 10 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 500 mg/tablet equivalent to 200 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 1 hour no more than 25%, after 2 hours no more than 40%, after 4 hours no more than 60%, after 8 hours no more than 90%.

EXAMPLE H

500 g of propionyl carnitine are dispersed in a granulator/kneader with 90 g of stearic acid and 40 g of carnauba wax, in which 20 g of diethylene glycol monoethyl ether had previously been melted. The system is heated to carry out the granulation of the active ingredient in the inert/amphiphilic matrix. The resulting 650 g of formulation are added with 60 g of hydroxypropyl methylcellulose and 10 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 720 mg/tablet equivalent to 500 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 40%, after 180 minutes no more than 60%, after 4 hours no more than 80%, after 8 hours no more than 90%.

EXAMPLE I

One kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with 200 g of cetyl alcohol and 25 g of glycerol palmitostearate the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30° C. The resulting inert matrix is added, keeping stirring and kneading during cooling, with 50 g of soy lecithin and 50 g of ethylene glycol monoethyl ether. The granulate is extruded through a metallic screen of suitable size and mixed with 50 g of hydroxypropyl methylcellulose, 1320 kg of maltodextrins, 2 kg of lactose-cellulose mixture, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to unitary weight of about 500 mg, having hardness suitable for being dissolved in the mouth and a pleasant taste.

EXAMPLE J

Operating as in the preceding example, chewable tablets are prepared replacing dextrin with mannitol and the lactose-cellulose mixture with xylitol. The resulting tablets have pleasant taste and give upon chewing a sensation of freshness enhancing the flavour.

EXAMPLE K

Operating as described in example I, but with the following components:

active ingredient: ibuprofen	*mg*	*100*
lipophilic/inert matrix component: cetyl alcohol	*mg*	*15*
amphiphilic matrix component: soy lecithin	*mg*	*8*
hydrophilic matrix components: mannitol	*mg*	*167*
maltodextrins	*mg*	*150*
methylhydroxypropylcellulose	*mg*	*30*
adjuvants: aspartame	*mg*	*15*
flavour	*mg*	*5*
colloidal silica	*mg*	*5*
magnesium stearate	*mg*	*5*

500 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the bitter, irritating taste of the active ingredient.

EXAMPLE L

Operating as described in example I, but with the following components:

active ingredient: diclofenac sodium	*mg*	*25*
lipophilic/inert matrix component: cetyl alcohol	*mg*	*5*
glycerol palmitostearate	*mg*	*5*
amphiphilic matrix component: soy lecithin	*mg*	*7*
hydrophilic matrix components: xylitol	*mg*	*168*
maltodextrins	*mg*	*150*
hydroxypropylmethylcellulose	*mg*	*20*
adjuvants: aspartame	*mg*	*5*
flavour	*mg*	*5*
colloidal silica	*mg*	*5*
magnesium stearate	*mg*	*5*

400 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE M

Operating as described in example I, but with the following components:

active ingredient: chlorhexidine	*mg*	*2.5*
lipophilic/inert matrix component: cetyl alcohol	*mg*	*0.5*
glycerol palmitostearate	*mg*	*0.5*
amphiphilic matrix component:	*mg*	*0.3*
diethylene glycol monoethyl ether hydrophilic matrix components: xylitol	*mg*	*38*
maltodextrins	*mg*	*96*
hydroxypropyl methylcellulose	*mg*	*10*
adjuvants: aspartame	*mg*	*3*
flavour	*mg*	*5*
colloidal silica	*mg*	*2*
magnesium stearate	*mg*	*2*

150 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE N

One Kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with g 125 of cetyl alcohol: the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30° C., then added with g 30 of lecithin. The resulting matrix is then extruded through a metallic screen of suitable size and mixed with 2.415 kg of lactose, 1.0 kg of maltodextrins, 50 g of hydroxypropyl methylcellulose, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to about 500 mg tablets, having hardness suitable for being dissolved in the mouth and pleasant taste.

The invention claimed is:

1. A controlled release and taste-masking oral pharmaceutical composition comprising:

budesonide as an active ingredient incorporated into a matrix structure consisting essentially of:

a) a lipophilic matrix consisting of lipophilic compounds with a melting point between 40° C. and 90° C. in which the active ingredient is at least partially inglobated;

b) an amphiphilic matrix;

c) an outer hydrophilic matrix consisting of hydrogels in which the lipophilic matrix and the amphiphilic matrix are dispersed; and

a gastro-resistant coating wherein the active ingredient is dispersed both in the hydrophilic matrix and in the lipophilic/amphiphilic matrix, and the composition is in the form of tablets, capsules or minitablets.

2. The composition according to claim **1**, wherein the active ingredient is mixed and at least partially inglobated in the amphiphilic matrix.

3. The composition according to claim **1**, wherein the active ingredient is mixed and at least partially inglobated in the lipophilic matrix.

4. The composition according to claim **1**, wherein the lipophilic matrix consists of C6-C20 alcohols or C8-C20 fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six.

5. The composition according to claim **1**, wherein the amphiphilic matrix consists amphiphilic compounds selected from the group consisting of polar lipids of type I or II, ceramides, glycol alkyl ethers, esters of fatty acids with polyethylene glycols, and diethylene glycols.

6. The composition according to claim **1**, wherein the lipophilic matrix consists of a compound selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, mono-, di- or triglycerides of fatty acids, the polyethoxylated derivatives thereof, waxes, and cholesterol derivatives.

7. The composition according to claim **1**, wherein the hydrophilic matrix consists of compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkylcellulose, carboxyalkylcellulose, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums, polyalcohols.

8. The composition according to claim **1**, wherein the gastro-resistant coating consists of acrylic and methacrylic acid polymers or copolymer or cellulose derivatives.

9. The composition according to claim **1**, further comprising bioadhesive substances.

10. The composition according to claim **1**, wherein the composition is in tablet form, and said tablet form is chewable or erodible in the buccal cavity or in the first portion of the gastrointestinal tract.

11. A method for the treatment a subject suffering from Inflammatory Bowel Disease and Irritable Bowel Syndrome, comprising administering an effective amount of the pharmaceutical composition according to claim **1** to a subject in need of such a treatment.

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